Towards optimal treatment of cancer related symptoms

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Elisabeth Cornelia Wilhelmina Neefjes

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TOWARDS OPTIMAL TREATMENT OF CANCER RELATED SYMPTOMS

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INTRODUCTION

INTRODUCTION

Every year over 100,000 people in the Netherlands are diagnosed with cancer.[1] Through early diagnosis and advancing treatment options survival rates are improving, but still 45,000 Dutch patients die from cancer every year. Constituting 31.2% of all-cause mortality, cancer was the leading cause of death in the Netherlands in 2017.[2] In the period between diagnosis of an incurable disease and the moment of death patients receive palliative care. This palliative care phase varies in length from a number of days up to several years. During this period, treatment options are discussed with the patient with a focus on prolonging life, but more and more the focus shifts towards sustaining quality of life with supportive and/or palliative care.

The term palliative care is not used exclusively for patients with cancer. All patients suffering from a potentially life threatening disease are eligible to receive palliative care, for example patients suffering from cardiovascular heart disease, chronic obstructive pulmonary disease or dementia. To help clinicians decide for which patients palliative care is suitable the 'surprise question' has been introduced.[3,4] If the answer to the following question is 'no', it is likely that the patient is a candidate for palliative care; 'would you be surprised if this patient dies within a year'?

Palliative care is defined by the World Health Organization as follows: 'Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. Palliative care:

- provides relief from pain and other distressing symptoms;
- affirms life and regards dying as a normal process;
- intends neither to hasten or postpone death;
- integrates the psychological and spiritual aspects of patient care;
- offers a support system to help patients live as actively as possible until death;
- offers a support system to help the family cope during the patients illness and in their own bereavement;
- uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated;
- will enhance quality of life, and may also positively influence the course of illness;
- is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.'[5]

Several organizations, such as the National Comprehensive Cancer Network (NCCN) and Integraal Kankercentrum Nederland (IKNL) have developed guidelines on how to assess and treat the problems a patient might experience during the palliative care phase.[6,7] These guidelines focus on integrative care with attention to both psychological and social challenges as well as physical symptoms a patient might experience. The general method is to regularly screen for specific symptoms, and to implement supportive measures to alleviate the symptom(s) upon detection.

These measures include non-pharmaceutical and pharmaceutical options. If possible, measures should also be taken to prevent a symptom that can be anticipated. In these guidelines the lack of high quality evidence is highlighted, resulting in advices based on moderate to low-level evidence and consensus in the expert group writing the guideline.[6,7] Most frequent symptoms of patients with advanced cancer are fatigue, pain, dyspnea, insomnia, and loss of appetite (figure 1).[8,9]

In this thesis four frequent symptoms that have a major impact on quality of life will be discussed: delirium, (opioid induced) constipation, cancer related fatigue and chemotherapy-induced nausea and vomiting. [8-10]

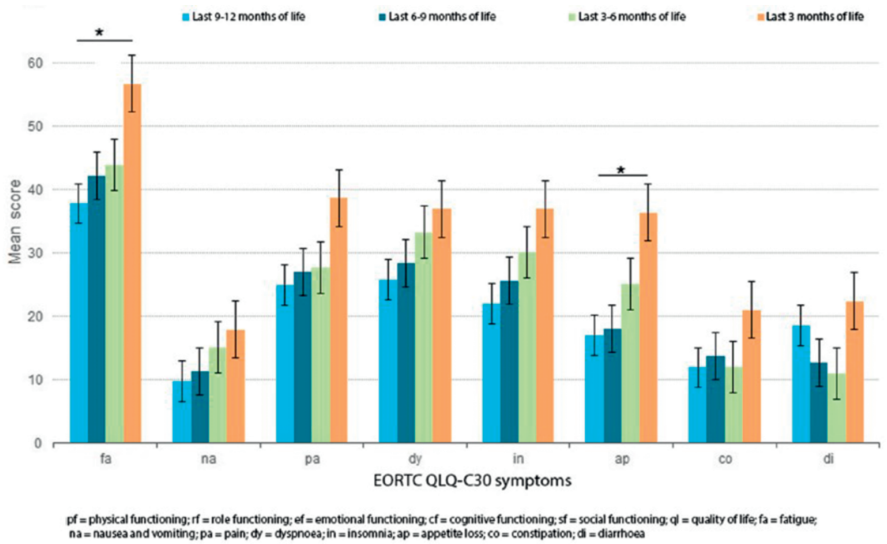

Figure 1. Symptoms affecting quality of life in the last year of life.[8] © reprint with permission

Delirium

Delirium is sometimes called acute confusion, which summarizes the clinical symptoms.[11] Delirium is a neuropsychiatric disorder that develops in a short period of time. It is characterized according to the DSM-5 criteria by

a. a disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
b. The disturbance develops over a short period of time (usually hours to a few days), represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
c. An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).
d. The disturbances in criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal such as coma.

e. There is evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.[12]

Delirium can present itself in a hyperactive form, with motoric restlessness, and in a hypo-active form where the patient seems more or less asleep and irresponsive to stimuli, or a mixture of both.[13] The threshold for the development of delirium is defined by predisposing and precipitating factors. For example, a young healthy patient will need far more harmful stimuli before developing delirium, than an older patient with Alzheimer and an alcohol addiction (figure 2).[14] In the dying phase, patients often develop a terminal delirium.[15] Because delirium hampers effective communication this is very distressing for both patients and relatives.[10,15]

Patients with cancer admitted to the hospital are expected to have both predisposing and precipitating factors for delirium, and therefore have a high risk of developing delirium. In chapter 2 the characteristics of patients admitted to the medical oncology ward of a tertiary care hospital are studied with respect to their relation to the development of delirium. The most discriminating characteristics will be used to build a prediction model for delirium. Patients identified to have a high risk of developing delirium should be regularly screened for symptoms of delirium. Ideally, delirium screening should be performed by nurses, as they have more frequent contact with patients than physicians. This also provides the opportunity to observe fluctuations in the patients' behavior over time. In chapter 3 the reliability of a nurse rated screening instrument is tested for its use in patients with advanced cancer.

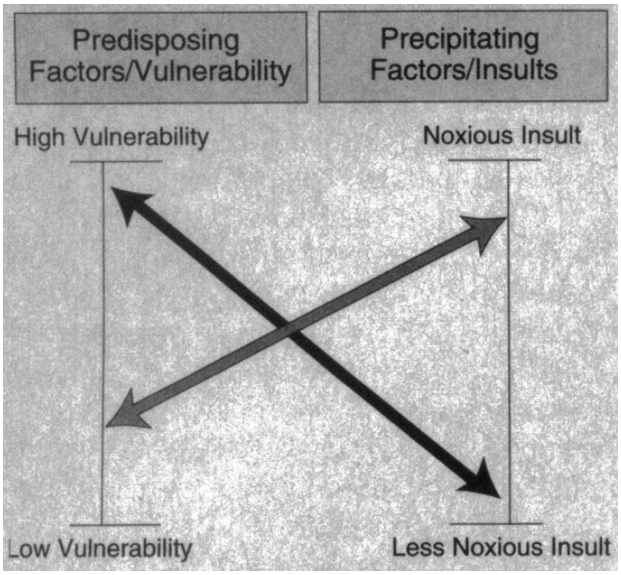

Figure 2. Predisposing and precipitating factors for delirium.[14] © reprint with permission

When a patient is diagnosed with delirium several actions should be taken. First of all, the precipitating factor(s) should be identified and treated if possible. At the same time non-pharmacological and sometimes pharmacological interventions should be implemented to alleviate the delirium symptoms.[6,16] Examples of non-pharmacological interventions are to ask family members to stay with the patient to calm them down and help them orientate in time and space, to provide a clearly defined day and night rhythm with activities during the day and dimmed lights in the night, and to restrict the use of iv lines and urinary tract catheters to the bare minimum. Pharmacological measures include the elimination of possible drugs that may precipitate the development of delirium, but also the use of anti-psychotic drugs (and sometimes benzodiazepines). The most frequently used drug for delirium treatment is the typical antipsychotic drug haloperidol.[6,16] Efficacy of this drug is about 50 percent, and side effects such as tremors and sedation can be limiting factors for its use.[17] In the treatment of psychotic diseases atypical antipsychotics have shown fewer side effects than haloperidol,[17] and in a retrospective study by Breitbart et al, the efficacy of the atypical drug olanzapine has been suggested to be about 75%.[18] In chapter 4 we performed a randomized clinical trial to compare the efficacy of olanzapine to haloperidol in the treatment of delirium in patients with advanced cancer.

Opioid induced constipation

Many patients with cancer will need opioids to relieve pain.[19] One of the side effects of opioid treatment is opioid induced constipation.[19,20] This is thought to be caused by the activation of the mu-receptor in the gut by opioids, where the pain relieve is caused by the effects of opioids on the mu-receptor in the central nerve system.[20] Methylnaltrexone is a drug that has been developed to inhibit activation of the mu-receptor in the gut, while activation of the mu-receptor in the central nerve system is still possible because this drug does not cross the blood-brain barrier.[20] It is registered to treat opioid-induced constipation if not responsive to regular laxative treatment.

The variation in opioid subtypes is based on their affinity for the different opioid receptors and their distribution profile (peripheral vs. central nerve system). This results in differences in their effect on the mu-opioid receptor in the gut, and could possibly affect the prevalence of opioid-induced constipation, and the efficacy of methylnaltrexone in the treatment of opioid-induced constipation.

In chapter 5 and 6 of this thesis a description is given of the prevalence and treatment of opioid induced constipation in daily practice at the oncology department. Furthermore, the study design and results of a trial looking into the effect of methylnaltrexone in patients using different opioid subtypes are described.

Cancer related fatigue

Patients with cancer often complain of cancer related fatigue as one of the most debilitating symptoms. It influences their resilience to treatment side effects and has a negative impact on their quality of life during and after treatment.[21] In chapter 7 of this thesis, a description is given of the possible causes of cancer related fatigue and the treatment options studied thus far. In

chapter 8, the association between cancer related fatigue and skeletal muscle mass is studied to explore whether efforts to increase muscle mass are a viable treatment option for patients suffering from CRF.

CINV

Chemotherapy-induced nausea and vomiting are for many patients the most feared side-effects of cancer treatment.[22,23] In the past years many (prophylactic) treatment options have been developed to reduce CINV.[24] These drugs have been extensively tested in patients receiving highly emetogenic chemotherapy.[24] Much less is known about the effect of these drugs in moderately emetogenic chemotherapy. In chapter 9 a systematic review of the evidence concerning prophylactic treatment for CINV in moderately emetogenic chemotherapy is performed forming the basis for a currently ongoing randomized clinical trial comparing different treatment strategies for CINV in moderately emetogenic chemotherapy (Netherlands Trial Register NL38215.029.11).

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2

IDENTIFICATION OF PATIENTS WITH CANCER WITH A HIGH RISK TO DEVELOP DELIRIUM

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ABSTRACT

Background

Delirium deteriorates the quality of life in patients with cancer, but is frequently underdiagnosed and not adequately treated. In this study, we evaluated the occurrence of delirium and its risk factors in patients admitted to the hospital for treatment or palliative care in order to develop a prediction model to identify patients at high risk for delirium.

Methods

In a period of 1.5 years, we evaluated the risk of developing delirium in 574 consecutively admitted patients with cancer to our academic oncology department with the Delirium Observation Screening Scale. Risk factors for delirium were extracted from the patient's chart. A delirium prediction algorithm was constructed using tree analysis, and validated with fivefold cross validation.

Results

574 patients with cancer were acutely (42%) or electively (58%) admitted 1733 times. The incidence rate of delirium was 3.5 per 100 admittances. Tree analysis revealed that the predisposing factors of an unscheduled admittance and a metabolic imbalance accurately predicted the development of delirium. In this group the incidence rate of delirium was 33 per 100 patients (1:3). The AUC of the model was .81, and .65 after five-fold cross-validation.

Conclusions

We identified that especially patients undergoing an unscheduled admittance with a metabolic imbalance do have a clinically relevant high risk to develop a delirium. Based on these factors, we propose to evaluate preventive treatment of these patients when admitted to the hospital in order to improve their quality of life.

INTRODUCTION

Delirium is a common problem in hospital care, especially for patients with cancer as well as elderly and frail patients.[1] It is a syndrome of brain dysfunction characterized by a disturbance in attention, awareness, and cognition, with a rapid onset that is caused by an underlying medical condition.[2,3] The occurrence of delirium depends on a combination of vulnerability (predisposing factors) and precipitating factors, that trigger the development of delirium.[4] Risk factors include aging, cognitive impairment and a history of delirium, and screening for delirium in patients at risk may be of help to reduce suffering from delirium.[5-11]

Data on the incidence and prevalence of delirium in literature range from a five percent prevalence rate upon admission to a geriatric hospital ward[12] up to an incidence rate of 88 percent in patients dying from cancer.[8] This diversity in incidence and prevalence rates indicates that it is a serious problem for patients with cancer especially when terminally ill.

In recent publications it has been suggested that prophylactic treatment with antipsychotics should be considered to prevent delirium,[13-17] but due to the varying incidence rates of delirium and the sometimes severe side-effects of these medicines (primarily haloperidol)[18] there is reluctance to apply preventive treatment to all patients with cancer admitted to the hospital.

It would be of clinical significance if one could determine which patients are likely to develop delirium at admission in order to select patients who might benefit from prophylactic treatment.

In this study, the primary aim was to evaluate the occurrence of delirium and its risk factors in patients with cancer admitted to the hospital for treatment or palliative care in order to develop a prediction model to identify patients at high risk for delirium.

METHODS

This retrospective study was conducted in all patients with solid malignancies admitted to our medical oncology ward of the VUmc Cancer Center Amsterdam (CCA), VU University Medical Center, between Jan 1st 2011 and June 30th 2012. For each patient the following data were collected from medical charts: baseline characteristics, presence of delirium and its risk factors throughout the entire admission. The study was conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Because of the retrospective character of this study no additional informed consent could be obtained and a waiver was obtained from the medical ethical committee.

Screening for delirium was performed twice a week during three consecutive nursing shifts according to standard hospital procedures using the Delirium Observation Screening Scale (DOSS).[12] The DOSS is a validated 13-item nurse rated screening instrument for delirium that is commonly used in Dutch hospitals. Scores range from 0 to 13 points, with ≥ 3 as a cut-off for delirium. It has sensitivity and specificity rates of 92 and 82 percent, respectively.[19] Delirium was recorded as present if the diagnosis was noted in the patient chart, or if the patient had a DOSS score ≥ 3 without a rejection of the delirium diagnosis written down in the chart.

The following risk factors were assessed: Age > 70 years, alcohol or drug abuse, hearing, visual and/or cognitive impairment, history of delirium, high doses of opioids (>90mg of oral morphine or equivalent), corticosteroids (>15mg dexamethasone or equivalent) and/or sedatives (>2mg lorazepam or equivalent), infections, postoperative state (until discharge of major surgery), constipation (note of constipation or note of delayed stool production for >48 hours), urinary retention, tumor burden and location, organ failure and metabolic disturbances.[4-10] In detail these risk factors are depicted in table 1. To avoid dependence the first admission with or without delirium for each patient was used for comparisons.

Development of a delirium prediction algorithm

Based on the predisposing factors and the grouped variables for the precipitating factors a prediction algorithm was developed. For the development of this prediction algorithm, the groups were defined irrespective of the prevalence rates of the individual factors to limit the number of factors included (see Table 1). Grouped variables were defined positive if any of the factors in this group was present. Eastern Co-operative Oncology Group (ECOG) performance status (0-2 vs. 3-4), palliative or curative treatment intention, and whether or not an admission was scheduled, were also included in the prediction algorithm. For prediction models, it is recommended that the number of events should ideally be 10-fold higher than the number of variables included in the model.[20] Therefore, we enriched the database with 46 extra delirium cases that were consecutively diagnosed with DOSS screening between July 2012 and September 2013 (Table 2). The baseline characteristics of these cases did not significantly differ from the patients with delirium in the original dataset. The enriched database is suitable for the calculation of odds ratios and the identification of predictors, but not for the calculation of absolute risks.[21] The absolute risks were calculated from the original database.

Statistical analysis

Statistical evaluation of differences between non-delirious and delirious patients was performed with a χ^2-test, the Fisher exact test, or the students t-test, whenever appropriate. Because of the multiple comparisons an adjusted *P*-value of .01 was considered statistically significant. To create a delirium risk prediction algorithm that can be easily implemented in the clinic we used a tree analysis method.[22] All predisposing and the grouped precipitating factors for delirium were used in this tree analysis, irrespective of the χ^2-test and students t-test results, to predict the risk of developing delirium in subgroups of patients. The number of splits in the tree was chosen in order to minimize the cross-validated prediction error. Five-fold cross-validation was used for validation of the algorithm. For both the original and the cross-validated model the area-under-the-curve (AUC) was calculated. Data were collected in the web-based database system OpenClinica version 3.1.2. Statistical tests were performed with SPSS version 20.0. The prediction algorithm was constructed with the software package R program Rpart (version 3.1).

Table 1. Predisposing and precipitating factors for delirium

Predisposing factors		
Age > 70 years Alcohol or drug abuse Hearing impairment Visual impairment History of delirium Cognitive impairment		
Precipitating factors		
Group	**Factor**	**Cut-off**
High doses of psychotropic medication	Opioids Corticosteroids Sedatives	> 90 mg morphine per day or equivalent > 15 mg dexamethasone per day or equivalent > 2 mg lorazepam per day or equivalent
Withdrawal	Alcohol Sedatives Other	
Infection	Fever Sepsis Urinary tract infection Pulmonary tract infection Other infections	>38.5 °C
Postoperative state		
Constipation		
Urinary retention		
Intracranial neoplasm	Primary tumor Metastasis Carcinomatous meningitis	
Organ failure	Pulmonary failure Renal insufficiency Liver failure Cardiac failure	O_2 sat < 88% or PO_2 < 55 mm Hg creatinine > 312 mmol/liter (3xULN) or creatinine > 3 x baseline Bilirubin > 60 mmol/liter (3x ULN) and/or ASAT > 150 U/liter (5x ULN) and/or ALAT > 200 U/liter (5x ULN) Requiring (prolonged) hospitalization
Metabolic disturbance	Calcium (corrected for albumin level) Sodium Potassium Glucose Albumin	< 1.75 mmol/liter > 3.1 mmol/liter < 130 mmol/liter > 155 mmol/liter < 3.0 mmol/liter > 6.0 mmol/liter < 2.2 mmol/liter > 13.9 mmol/liter < 20 g/liter

Table 2. Patients included in prediction algorithm

	Delirium *n* =	No delirium *n* =	Total *n* =
Study period	52	522	574
Extra delirium cases[a]	46	-	46
Total	98	522	620

[a] For adequate power in the development of the delirium prediction algorithm, data on the predisposing and precipitating factors of 46 patients who developed delirium between July 2012 and September 2013 were added to the original dataset. These data were only used for the development of this algorithm. Absolute risks at delirium reported in the article were calculated with the original dataset.

RESULTS

574 individual patients were admitted 1733 times during the study period (mean 2.95 admittances per patient, ranging from one to 22 admissions per patient). Sixty delirium episodes were recorded for 52 individual patients, which resulted in a delirium incidence rate of 3.5 per 100 admittances. Nine percent of all patients admitted in this period developed delirium.

Patient characteristics

Of all 1733 admittances, 1003 admittances (57.9%) were scheduled. The mean age of admitted patients was 60 years (SD 13.1) and 60 percent of the patients were male. Compared with patients who did not develop delirium, patients who developed delirium were significantly older (mean age of 59 versus 67 years respectively (P<.001)), had a worse ECOG performance status at admittance and more often received treatment with palliative intention or palliative care only. Ninety-four percent of the patients who developed delirium had an unscheduled admittance, compared to 49 percent of the patients who did not develop delirium (P<.001). In ten of the 730 unscheduled admittances the indication for the admittance was suspected delirium (n=2), confusion (n=5), or drowsiness (n=3). Seven of these patients were diagnosed with delirium in the hospital. Patients with delirium stayed longer in the hospital, and the outcome was worse. In Table 3, these data are shown in detail.

Predisposing and precipitating factors

The most prevalent predisposing factors in this group of patients were age >70 and alcohol/drug abuse (21 and 8 percent, respectively). Although all factors were previously defined as predisposing factors, only age >70 significantly correlated with the development of delirium in univariate analysis (P<.001).

The most prevalent precipitating factors were high doses of psychotropic medication, infection, constipation, and metabolic imbalance (25, 22, 19, and 18 percent respectively). The precipitating factors infection, constipation, urinary retention, organ failure, and metabolic imbalance were significantly related with the presence of delirium (P<.001) (Table 4).

Delirium prediction algorithm

To determine the most relevant factors for the risk at delirium, a prediction algorithm by using tree analysis was developed using the enriched database. The optimum number of splits, with the lowest cross-validated prediction error, was four.

The absolute risks in the decision tree, obtained by projecting the algorithm to the original, non-enriched dataset, are depicted in Figure 1. A patient admitted to the hospital ward has a risk of 9 percent to develop delirium (95%-CI: 6.8-11.7%). The first factor that made a major distinction between a low risk at delirium (1.1% in the original dataset, 95%-CI: 0.2-3.2%) and an intermediate risk at delirium (16% in the original dataset, 95%-CI: 12-21%) was whether or not an admission was scheduled. Due to the very low risk at delirium (1:100), it was deemed unnecessary to make any further distinctions within the group with a scheduled admittance. In the group with an emergency admission, a further distinction could be made between patients that did or did not have metabolic imbalances. These patients had a delirium risk of 10 and 32.5 percent, respectively (95%-CI: 6-15%, resp. 22-44%). In the group with an unscheduled admittance combined with a metabolic imbalance (delirium risk 1:3), ECOG performance status 0-2 vs. ≥3, and curative vs. palliative treatment intention were further splits. The AUC of this algorithm was .81 (Figure 2 upper line). We evaluated predictive validity of the algorithm by five-fold cross-validation. This provided a lower estimate for the AUC of .65 (Figure 2 lower line), as the original algorithm estimates do not correct for uncertainty in the selection of predisposing and/or precipitating factors. The sum of the sensitivity and specificity was maximal at a cut-off with a high specificity of 85%, and a lower sensitivity of approximately 40% in the cross-validated algorithm. This cut-off allows for identification of a subgroup of patients with a high risk at delirium. In the algorithm, the cut-off is the distinction between patients with an unscheduled admittance with or without metabolic imbalances.

We evaluated whether the factors found in this algorithm were also predictive for different admissions of the same patient by comparing the prevalence of unscheduled admittances and metabolic imbalances within patients who had both an admittance with delirium and an admittance without delirium (27/52 patients with delirium). Admittances with delirium were significantly more often unscheduled than admittances without delirium (25/27 vs. 10/27, $P<.001$). Metabolic imbalances were also more prevalent in the delirium admittance than in the admittance without delirium, but this difference was not statistically significant (12/27 vs. 6/27, $P=.08$). During the admittance with delirium, patients had a higher chance to be in the high-risk group according to the prediction algorithm (with the combination of an unscheduled admittance and metabolic imbalances), than during the admittance without delirium (12/27 resp. 4/27, $P=.02$).

DISCUSSION

In this study, medical data from 574 patients during 1733 admittances were evaluated to determine the occurrence of delirium and its risk factors in patients admitted to the hospital for treatment or palliative care. We found a delirium incidence rate of 3.5 per 100 admittances and determined that nine percent of all patients admitted in this period developed delirium. The most frequent predisposing factors in this group of patients were age >70 and alcohol/drug abuse, while the most

Table 3. Patient characteristics

		Total ***n*=1733**	**%**	**Total first admittance** ***n*=574**	**%**
Age	Mean (SD)	57.2 (14.2)		60.0 (13.1)	
Sex	M : F	1076:657	62:38	345:229	60:40
Tumour type	Gastro-intestinal	645	37	196	34
	Genito-urethral	369	21	129	22
	Skin	50	3	34	6
	Lung	2	0	2	0
	Head & Neck	369	21	108	19
	Brain	8	1	6	1
	Sarcoma	120	7	20	4
	Breast	97	6	53	9
	Other	73	4	26	5
ECOG performance status	0	223	13	96	17
	1	964	56	262	46
	2	385	22	146	25
	3	132	8	56	10
	4	29	2	14	2
Length of stay	Days (Median (IQR))	3 (2-6)		4 (2-7)	
Outcome	Alive	1692	98	549	96
	Deceased	41	2	25	4
Treatment intention	Curative	626	36	174	30
	Palliative	1107	64	400	70
Indication for admittance	Scheduled admittance	1003	58	270	47
	Chemotherapy	885	51	209	36
	Diagnostic procedures	68	4	40	7
	Intervention	50	3	21	4
	Unscheduled admittance	730	42	304	53
	Clinical symptoms	535	31	251	44
	Complication	195	11	53	9
Delirium Type	Hyperactive				
	Hypo-active				
	Mixed				
	Unknown[b]				

[a] p-values of the comparison between the patients with delirium and the patients without delirium

[b] delirium type could not be determined from the information in the patient chart

No delirium *n*=522	%	Delirium *n*=52	%	*P*=[a]	OR	95%-CI of OR
59.3 (13.3)		68 (8)		<.001		
313:209	60:40	32:20	62:39	.83	1.068	.595-1.919
179	34	17	33			
119	23	10	19			
25	5	9	27			
2	0	0	0			
100	19	8	15			
4	1	2	4			
20	4	0	0			
48	9	5	10			
25	5	1	2	.009		
96	18	0	0			
252	48	10	19			
127	24	19	37			
40	8	16	31			
7	1	7	14	<.001		
4 (2-7)		10 (5-16)		<.001		
508	97	41	79			
14	3	11	21	<.001	9.735	4.155-22.809
166	32	8	15			
356	68	44	85	.01	2.067	1.079-3.958
267	51	3	6			
208	40	1	2			
39	7	1	2			
20	4	1	2			
255	49	49	94	<.001	17.102	5.264-55.560
209	40	42	81			
46	9	7	14			
		11	21			
		20	39			
		18	35			
		3	6			

Table 4. Prevalence of predisposing and precipitating factors

		Total *n*=574	%	No delirium *n*=522	%	Delirium *n*=52	%	*P*=	Odds Ratio	95% confidence interval OR
Predisposing factors										
Age >70	No	452	79	421	81	31	60			
	Yes	122	21	101	19	21	40	<.001*	2.824	1.557-5.119
Alcohol/drug abuse	No	526	92	480	92	46	89			
	Yes	48	8	42	8	6	12	.43	1.491	.602-3.693
Hearing difficulty	No	556	97	508	97	48	92			
	Yes	18	3	14	3	4	8	.07	3.024	.958-9.549
Visual impairment	No	559	97	511	98	48	92			
	Yes	15	3	11	2	4	8	.04	3.871	1.187-12.624
History of delirium	No	569	99	517	99	52	100			
	Yes	5	1	5	1	0	0	.99	-	-
Cognitive impairment	No	562	98	514	99	48	92			
	Yes	12	2	8	2	4	8	.02	5.354	1.555-18.431
Precipitating factors										
High doses of psychotropic medication	No	428	75	397	76	31	60			
	Yes	146	25	125	24	21	40	.01	2.151	1.193-3.878
	Corticosteroids	43	7	43	8	0	0	.03	-	-
	Sedatives	29	5	22	4	7	14	.01	3.535	1.432-8.727
	Opioids	86	15	70	13	16	31	.002*	2.870	1.513-5.445

Table 4. (continued)

			Total *n*=574	%	No delirium *n*=522	%	Delirium *n*=52	%	*P*=	Odds Ratio	95% confidence interval OR
Alcohol/drug withdrawal	No		561	98	511	98	50	96			
	Yes		13	2	11	2	2	4	.33	1.858	.401-8.619
		Alcohol	12	2	11	2	1	2	.99	.911	.115-7.199
		Sedatives	0	0	0	0	0	0	-	-	-
		Other	2	0	1	0	1	2	.17	10.216	.630-165.771
Infection	No		448	78	425	81	23	44			
	Yes		126	22	97	19	29	56	<.001*	5.524	3.062-9.966
		Fever	48	8	39	7	9	17	.03	2.587	1.175-5.694
		Sepsis	16	3	9	2	7	14	<.001*	8.849	3.148-24.879
		Urinary tract	30	5	22	4	8	15	.003*	4.124	1.735-9.803
		Respiratory tract	26	5	17	3	9	17	<.001*	6.205	2.610-14.750
		Other	30	5	23	4	7	14	.01	3.368	1.370-8.279
Intracranial neoplasm	No		538	94	494	95	44	85			
	Yes		36	6	28	5	8	15	.01	3.208	1.379-7.461
		Primary tumour	8	1	5	1	3	6	.03	6.331	1.469-27.287
		Metastasis	24	4	19	4	5	10	.06	2.816	1.006-7.885
		Carcinomatous meningitis	4	1	4	1	0	0	.99	-	-
Post-operative state	No		557	97	509	98	48	92			
	Yes		17	3	13	2	4	8	.06	3.263	1.024-10.398
Constipation	No		468	82	433	83	35	67			
	Yes		106	19	89	17	17	33	.006*	2.363	1.268-4.405
Urinary retention	No		560	98	514	99	46	89			
	Yes		14	2	8	2	6	12	.001*	8.380	2.788-25.192

Table 4. (continued)

		Total ***n*=574**	**%**	**No delirium** ***n*=522**	**%**	**Delirium** ***n*=52**	**%**	***P*=**	**Odds Ratio**	**95% confidence interval OR**
Organ failure	No	476	83	447	86	29	56			
	Yes	98	17	75	14	23	44	<.001*	4.727	2.596-8.608
Liver failure	Not measured	77	13	70	13	7	13			
	No	437	76	401	77	36	69			
	Yes	60	10	51	10	9	17	.09	1.971	.898-4.326
	bilirubin >60 mmol/l	19	4	15	3	4	21	.08	2.849	.903-8.983
	ASAT >150	51	10	43	10	8	18	.12	2.062	.902-4.710
	ALAT >200	24	5	21	5	3	7	.47	1.469	.421-5.131
Pulmonary insufficiency	Not measured	380	66	361	69	19	37			
	No	173	30	148	28	25	48			
	Yes	21	4	13	2	8	15	.01	7.133	2.806-18.133
Renal failure	Not measured	15	3	15	3	0	0			
	No	543	95	497	95	46	88			
	Yes	16	3	10	2	6	12	.002*	6.696	2.327-19.239
Cardiac failure	No	565	98	514	98	51	98			
	Yes	9	2	8	2	1	2	.58	1.262	.155-10.294
Metabolic imbalance	Not measured	20	3	20	4	0	0			
	No	453	79	428	82	25	48			
	Yes	101	18	74	14	27	52	<.001*	6.538	3.599-11.878
	Calcium low	1/411	0	1/362	0	0/49	0	.99	-	-
	Calcium high	8/411	2	4/362	1	4/49	8	.009*	7.956	1.923-32.918
	Potassium low	30/550	5	21/498	4	9/52	9	.001*	4.754	2.051-11.022
	Potassium high	5/550	1	1/498	0	4/52	8	<.001*	41.417	4.538-378.011

Table 4. (continued)

		Total		**No delirium**		**Delirium**			**Odds**	**95% confidence**
		***n*=574**	**%**	***n*=522**	**%**	***n*=52**	**%**	***P*=**	**Ratio**	**interval OR**
	Sodium low	25/544	5	18/493	4	6/51	12	.02	3.519	1.330-9.311
	Sodium high	2/544	0	0/493	0	2/51	4	.009*	-	-
	Hypoglycaemia	1/395	0	0/350	0	1/45	2	.11	-	-
	Hyperglycaemia	24/395	6	19/350	5	4/45	9	.32	1.700	.551-5.240
	Albumin low	42/442	9	24/393	6	18/49	37	<.001*	8.927	4.378-18.206

* P<0.01

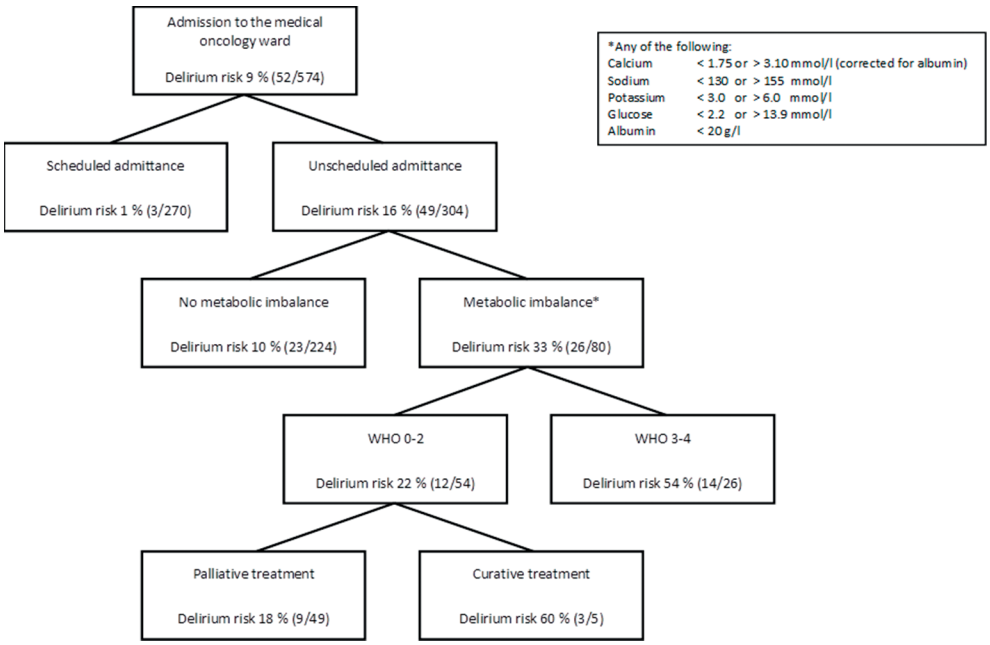

Figure 1. Delirium prediction algorithm. This risk is defined by the combination of factors mentioned in the boxes, starting with a baseline risk of 9% when a patient is admitted to the medical oncology ward. The * refers to the square in the corner of the figure in which the metabolic imbalances are defined.

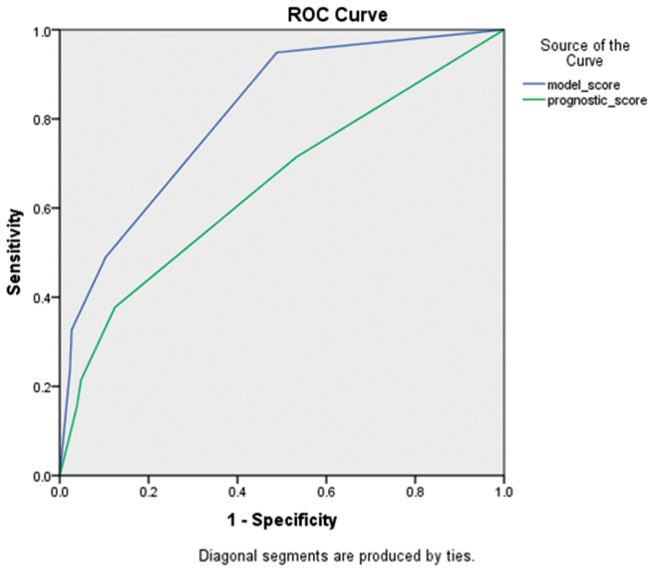

Figure 2. ROC curve of the prediction algorithm for delirium. These curves show the sensitivity and specificity of the different cut-off points in the algorithm. AUC of the original model (blue line) is .81 and .65 for the cross-validated model (green line).

frequent precipitating factors were high doses of psychotropic medication, infection, constipation, and metabolic imbalance.

Because of the large number of patients that were evaluated, it was possible to use both predisposing and precipitating factors to develop an algorithm that may be used in daily practice to identify patients with a high risk to develop a delirium.

The incidence rate of 3.5 percent per admittance in this evaluation is lower than the 16-18 percent reported on similar hospital wards.[6,9] A reason for the low incidence of delirium on this ward could be that half of the admittances were scheduled for patients to receive chemotherapy or undergo other interventions, as these patients have a low risk at delirium. In the study by Ljubisavljevic and Kelly (2003) these patients were not included, and it is likely that the proportion of scheduled admittances in the study by Gaudreau *et al* (2005) was also smaller. When all scheduled admissions are excluded from our dataset, the incidence rate of delirium goes up to 7.8 percent (57/730), which is still lower than in the aforementioned studies. Another important reason that might explain this low incidence rate could be that the mean age of the patients admitted to this ward was 60 years (only 21% of the patients were aged ≥70 years) and even the elderly patients had a good cognitive performance status, as only 2.1 percent of all patients had a cognitive impairment.

The selected predisposing and precipitating factors were previously defined for their significant relationship with delirium, but this relationship was not confirmed for all of these factors in this study. This is most likely due to the low prevalence rates of these risk factors. In other studies logistic regression analysis to determine the influence of an individual factor on a patients risk at delirium have been used.[8,23] Although the results of these analyses indicate that a patient in whom a certain factor is present has a relatively higher risk at delirium, it does not provide the clinician with a clinical tool to clearly define the absolute risk that a specific patient has to develop delirium. Also, the effect of a combination of multiple predisposing and/or precipitating factors in the same patient is often not clear. Therefore, a prediction algorithm could be of significant clinical value to provide this information. Martinez *et al* (2012) developed a prediction rule for patients admitted to the internal medicine ward.[24] This prediction rule could not be applied to our medical oncology ward as the prevalence of some of the components of the prediction rule was too low (e.g. age > 85 years).

We developed an alternative algorithm in which patients with high risk for delirium are rapidly identified based on an emergency admittance combined with metabolic imbalances (delirium risk 1:3) (see Figure 1). These factors are usually available upon admission of a patients with cancer and therefore this algorithm can be easily implemented in daily clinical practice. We here propose that based on this algorithm patients could be selected for preventive treatment for delirium.[12-16]

We do realize that our study has some limitations such as that it is a retrospective evaluation, the number of patients are rather limited to evaluate a high number (> 10) of predisposing factors for delirium, and although it concerns only patients with cancer, tumor diagnosis is heterogeneous. On the other hand, the strength of this study is that no selection has been made for patients with cancer acutely admitted to the hospital and that the algorithm to determine the risk at a delirium can be easily implemented in daily practice.

In future studies, preventive treatment for delirium should be evaluated for its influence on the quality of life of patients, while taking in account the added risk of treatment induced toxicity of such a treatment strategy. In addition, as previously advocated by others, we also highly recommend screening of acutely admitted patients for delirium.[25] The specificity for the cut-off in our algorithm is high (85%), but the sensitivity is only 40 percent. This means that 60 percent of the delirium cases would be missed when only attention is being focused at patients in the high-risk group. Therefore, while preventive treatment of patients identified by our algorithm with a high risk of delirium needs further evaluation, also screening for delirium symptoms in the other patients with an emergency admission should be considered.

In conclusion, delirium is a serious problem for patients with cancer admitted to the hospital. We identified that especially patients undergoing an unscheduled admittance with a metabolic imbalance do have a clinically relevant high risk to develop a delirium. Based on these factors, we propose to evaluate preventive treatment of these patients when admitted to the hospital in order to improve their quality of life.

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3

ACCURACY OF THE DELIRIUM OBSERVATIONAL SCREENING SCALE (DOS) AS A SCREENING TOOL FOR DELIRIUM IN PATIENTS WITH ADVANCED CANCER

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ABSTRACT

Background

The Delirium Observation Screening Scale (DOS) was developed to facilitate early recognition of delirium by nurses during routine clinical care. It has shown good validity in a variety of patient populations, but has not yet been validated in hospitalized patients with advanced cancer, although the DOS is commonly used in this setting in daily practice. The aim of this study was to evaluate the accuracy of DOS in hospitalized patients with advanced cancer using the revised version of the Delirium Rating Scale (DRS-R-98) as the gold standard.

Methods

Patients with advanced cancer admitted to the medical oncology ward were screened for delirium with the DOS and DRS-R-98. Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of the DOS were calculated, using a DOS score ≥3 as a cut-off for delirium.

Results

95 DOS negative and 98 DOS positive patients were identified. Sensitivity of the DOS, was >99.9% (95%-CI: 95.8-100.0%), specificity was 99.5% (95%-CI 95.5-99.96%), PPV was 94.6% (95% CI 88.0-97.7), and NPV was >99.9% (95% CI 96.1-100.0).

Conclusions

The DOS is an accurate screening tool for delirium in patients with advanced cancer. Since it has the benefit of being easily implicated in daily practice, we recommend to educate caregivers to screen patients with advanced cancer by DOS analysis. By early recognition and adequate treatment of this distressing delirium syndrome the quality of life of patients with advanced cancer can be improved.

Trial registration

ClinicalTrials.gov Identifier NCT01539733, Netherlands Trial Register NTR2559.

BACKGROUND

Delirium is the most common neuropsychiatric complication in patients with advanced cancer especially during hospitalization, with incidence rates ranging from 16% to 85%, depending on the stage of disease.[1-7] In a previous study from our group we found a higher number of patients with skin cancer and brain cancer in the group of patients with delirium compared to the patients without delirium.[8] Other studies showed conflicting results.[9,10] Therefore, there is no compelling evidence that delirium is more prevalent in certain cancer types. Because attention and awareness deficits impede the ability to communicate and participate in treatment decisions and symptom assessment, delirium has a negative influence on quality of life in a crucial phase at the end of life.[1] The presentation of delirium is quite variable among patients, and even within a given patient because of its waxing and waning course.[11] This hampers recognition and adequate treatment of delirium.[1] Therefore it is recommended to screen for delirium in patients with (advanced) cancer admitted to the hospital.[1,11] The diagnosis delirium should be made according to the DSM-criteria for delirium. Currently, version 5 is the most recent, but most screening and diagnostic instruments are based on the DSM-IV.[12] Efforts are being made to validate these instruments with the DSM 5 criteria.[13,14]

Available screening instruments which have been designed to be used by health care professionals for evaluating patients for possible delirium symptoms include: CAM,[15] NEECHAM Confusion Scale,[16] DOSS/DOS,[17,18] Nu-DESC,[5] ICDSC,[19] and PAED scale.[20] Some of these instruments have been designed to be used in a specific treatment setting like the ICU, whereas others focus on specific age groups, like children and adolescents. There is no specific screening instrument for delirium in patients with advanced cancer. A comparison between various features of the available screening and diagnostic instruments for delirium in adults was made by Grover and Kate in 2012.[12]

Delirium screening should be preferably performed by nurses because they have frequent contact with the patient throughout the day, and could therefore easily observe changes in the patient's attention and awareness over time, which is one of the main criteria for delirium according to the DSM 5 criteria.[21] The Delirium Observation Scale (DOS) appears to be the most suitable nurse-rated screening instrument for patients in general medical and surgical wards with a strong foundation in the DSM-IV criteria and good psychometric properties.[3,22] It can be assessed by nurses without specific training, and is experienced as user-friendly. A previous, small study by Detroyer *et al* suggests good sensitivity and specificity of the DOS in a palliative care population.[23] The aim of our study is to evaluate the diagnostic accuracy of the DOS as screening instrument for hospitalized patients diagnosed with advanced cancer.

METHODS

Patients

Hospitalized patients with advanced cancer admitted to the medical oncology ward of six sites (1 university cancer center, 3 teaching hospitals, 2 high-care hospices) in the Netherlands were recruited between January 2010 through December 2015. Patients and/or their legal representatives were asked for informed consent to participate in this diagnostic study, as part of a randomized

controlled trial (RCT), which compared the efficacy of haloperidol to olanzapine in case the patient was diagnosed with delirium (ClinicalTrials.gov identifier NCT01539733). The study was conducted according to Good Clinical Practice guidelines, the Declaration of Helsinki and local laws, and was approved by the institutional review boards of each participating study site.

Patients with any type of cancer in an advanced stage, of 18 years and older who were fluent in the Dutch language were considered eligible. Patients with pre-existing cognitive impairment (such as Alzheimer's disease), or psychiatric comorbidity that might hamper delirium diagnosis (e.g. schizophrenia) were excluded from this study. Also, patients using antipsychotic or neuroleptic medication for other reasons than neuropathic pain management were excluded. Additional exclusion criteria were based on contra-indications for the use of haloperidol or olanzapine, like high risk at alcohol withdrawal delirium, glaucoma, Parkinson's disease, QTc-interval prolongation >500msec at baseline ECG, a history of malignant neuroleptic syndrome and concomitant treatment with anti-convulsive drugs.

Study Assessments

Patients who were included in the trial were screened for delirium by their nurse using the DOS at the moment of admittance, and subsequently three times a day, biweekly during their stay in the hospital. Each DOS positive patient (DOS ≥3) was randomly matched with a DOS negative patient (DOS < 3) to evaluate the accuracy of the DOS. DOS positive patients and the randomly matched DOS negative patients were assessed with the Delirium Rating Scale-R-98 (DRS-R-98) by a trained independent assessor, who was blinded with regard to the DOS score of a patient.

To prevent duplication bias patients were excluded from the DOS negative group if they were included in the randomised treatment part of the study during a later admission.

DOS

The original version, the Delirium Observational Screening Scale (DOSS), consisted of a 25-item scale based on the *DSM-IV* criteria for delirium.[17] The scale was designed to capture early symptoms of delirium that nurses could observe during regular care. The scale was subsequently reduced to 13 observations, and is known as the Delirium Observation Scale (DOS).[18] Each item can be rated as normal (score, 0) or abnormal (score, 1). A total score of 3 or more points indicates delirium. Completion of the instrument requires less than 5 minutes. A small descriptive study evaluated the DOS in patients admitted to a palliative care unit.[23] The DOS was compared to the CAM and the Delirium Index and showed good psychometric properties. Moreover, it was experienced as user-friendly by the bedside nurses. Internal consistency, predictive validity, and concurrent and construct validity of the DOS were tested in two prospective studies in high risk groups: geriatric medicine patients and elderly hip fracture patients.[18] The DOS has high internal consistency (0.96) and high content validity (α = 0.93). In these study groups the DOS scale had a sensitivity of 89-100% and a specificity of 68-88%. The positive predictive value was 47%, the negative predictive value was almost 100%. The DOS was also able to measure severity of delirium in geriatric patients.[24] Moreover, the DOS proved to be a good instrument to facilitate early recognition of delirium in

patients who undergo cardiac surgery: the sensitivity and specificity of the DOS was 100% and 96.6% respectively.[25]

DRS-R-98

The DRS-R-98 is a revised version of the Delirium Rating Scale.[26,27] The DRS-R-98 consists of 13 severity items that are scored from 0 (not present) to 3 points (severely present), and three diagnostic items, all of which are rated over the past 24 hours. Severity scores range from 0 to 39, and total scores range from 0 to 46. The DRS-R-98 is designed to be completed by a trained professional and takes about 10 to 15 minutes to complete.[27] The DRS-R-98 has a high internal consistency (0.90) and when using a cut-off of 17.75 points on the total scale a sensitivity of 92% and specificity of 95%.[27] Inter-rater-consistency was high in the validation study by Trzepacz *et al* (0.99).[27] The DRS-R-98 severity scale has the great benefit that it can be used for repeated measurements to assess the response to delirium treatment.[27] Recently, the DRS-R-98 has been validated for the new DSM-5 criteria.[28] The DRS-R-98 was chosen as a gold standard to evaluate the accuracy of the DOS because of its good psychometric qualities, because it has been validated in a palliative care setting, and is available in the Dutch language (the first language of the included patients and the researchers in this study group).[27]

Statistics

A sample size calculation was conducted to determine an 80% power in demonstrating that the DOS has a sensitivity of at least 90%. A sample of 100 patients per group (DOS positive vs. DOS negative) was needed when the sensitivity of the DOS was assumed to be 95%.[18,25]

Primary endpoints to assess the accuracy of the DOS are the sensitivity and specificity of the DOS score compared with the DRS-R-98 as the gold standard. Sensitivity, specificity, negative and positive predictive value are reported with 95% confidence intervals, calculated with the Wilson method.[29] Analyses will be corrected for partial verification, because only a proportion of DOS negative patients admitted to the study sites were included in this study. For the baseline characteristics standard descriptive statistics were used. Statistical analyses were performed with IBM SPSS version 22.0 (IBM, Armonk, NY, USA).

RESULTS

Between January 2010 and December 2015, 100 consecutive DOS negative and 95 DOS positive patients were included in the study. One DOS positive patient withdrew consent for participating in the study while recovering from delirium. Four DOS negative patients were included in the DOS positive group during a later hospital admission. These patients were excluded from the DOS negative group during the analyses. For one patient in each group all data were missing, leading to a total of 94 DOS negative and 93 DOS positive patients (Figure 1). The demographic and clinical characteristics are described in Table 1. The mean (SD) age was 68 (11) in the DOS positive group and 60 (13) in the DOS negative group ($p<0.001$). Other characteristics obtained at baseline were not significantly different between the groups. None of the patients in the DOS negative group

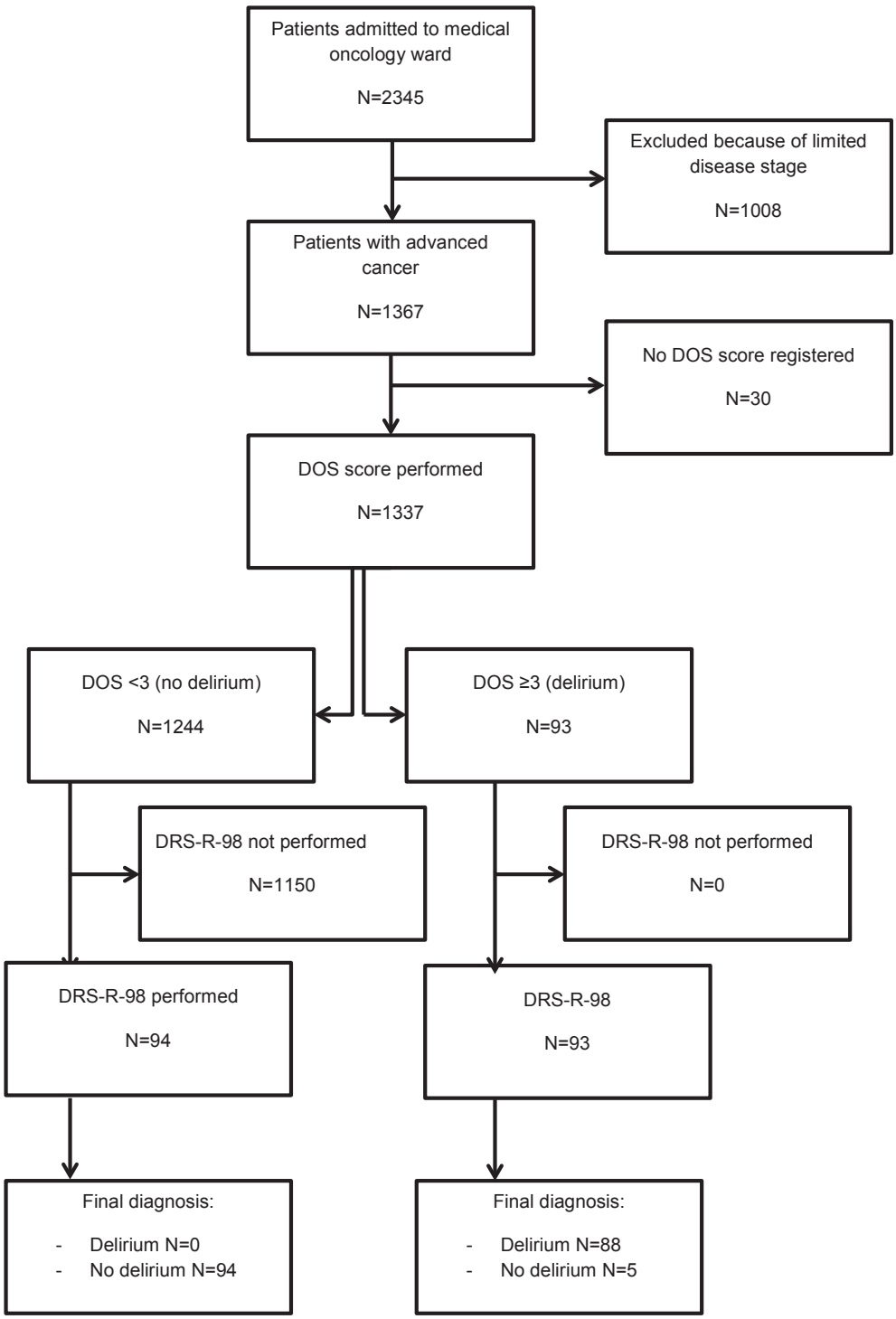

Figure 1. Study flow chart

Table 1. Baseline characteristics

		DOS negative N=94 (SD or %)	DOS positive N=93 (SD or %)	p
Age		60 (12.9)	68 (11.1)	<.001
Gender	Male	58 (62%)	66 (71%)	
	Female	36 (38%)	27 (29%)	.180
Tumor type	Gastro-intestinal	40 (43%)	28 (30%)	
	Breast	6 (6%)	6 (7%)	
	Genito-urethral	23 (25%)	29 (32%)	
	Skin	4 (4%)	8 (9%)	
	Lung	0	3 (3%)	
	Head&neck	5 (5%)	2 (2%)	
	Brain	0	2 (2%)	
	Sarcoma	4 (4%)	1 (1%)	
	Hematological	1 (1%)	9 (10%)	
	Other	11 (12%)	5 (5%)	.484
Brain metastasis	No	89 (95%)	87 (94%)	
	Yes	5 (5%)	6 (6%)	.767

Baseline characteristics of the patients in this study. No statistically significant differences were found except for age; Delirium Observational Scale (DOS) positive patients, who screened positive for delirium with a score ≥ 3 on this scale, tended to be older than DOS negative patients.

were diagnosed with delirium. Eighty-eight of the patients in the DOS positive group were diagnosed with delirium, see Table 2. The sensitivity and specificity of the DOS were >99.9% (95%CI: 95.8-100.0%) and 99.6% (95%CI: 95.5-100.0%) respectively, the negative predictive value (NPV) was 94.6 (95%CI: 88.0-97.7%), and the positive predictive value (PPV) was >99.9% (95%CI: 96.1-100.0%), see Table 3.

The median DOS score of the DOS positive patients was 4.0 (IQR 4.0-6.0). Higher DOS scores correlated with higher DRS-R-98 total scores, see Table 4.

Four of the five patients with a DOS of 3 or higher who were not confirmed to be delirious by the DRS-R-98 score (score <17.75), had DRS-R-98 total scores >12 points. The latter cut-off has been used as a more inclusive cut-off for delirium in some studies.[30,31] One patient scored being delirious on the DOS but only scored three points on the DRS-R-98. We speculate that he/she may have displayed only temporarily signs of delirium which had resolved by the time the DRS-R-98 was conducted.

DISCUSSION

To our knowledge this is the first study to evaluate the accuracy of the DOS in a large group of patients with advanced cancer. Our data showed that the DOS is a very sensitive and specific instrument to screen for delirium in hospitalized patients with advanced cancer. It might also give an impression of the delirium severity.

Table 2. DOS vs. DRS-R-98

	DRS-R-98 no delirium (<17.75)	DRS-R-98 delirium (≥17.75)	Total
DOS no delirium (<3)	94	0	94
DOS delirium (≥3)	5	88	93
Total	99	88	

Distribution of the results of the DOS and DRS-R-98 scores.

Table 3. Accuracy of the DOS

	Accuracy of the DOS	Wilson Score 95%CI lower limit	Wilson Score 95%CI upper limit
Sensitivity	1	0.958184	1.000004
Specificity	0.995997	0.955293	0.99966
PPV	0.946237	0.880258	0.976826
NPV	1	0.960748	1.000004

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the DOS, with 95% confidence intervals (95% CI) calculated by the Wilson method.

Table 4. DRS scores in DOS positive patients

DOS score	N=	DRS-R-98 total score median	DRS-R-98 total score IQR
3-4[a]	50	22.3	19.0-24.1
>4-6[b]	23	23.5	21.5-26.0
>6[c]	20	26.0	21.8-27.4

Distribution of the DRS-R-98 scores in patients screened positive for delirium with the DOS. When comparing the absolute DOS score to the DRS-R-98 total score a linear association was found; B 0.677, 95% CI .229-1.126, P0.004.
a. 1st and 2nd quartile
b. 3rd quartile
c. 4th quartile

Compared to other screening instruments, such as the CAM,[15] NEECHAM Confusion Scale,[16] and the Nu-DESC,[5] the DOS has shown better sensitivity and specificity. It has the benefits that it is quick to administer, and does not require training.[12]

Strengths of the study are that we were able to include a large group of patients, and that the DRS-R-98 assessment was performed by an independent assessor who was blinded to the DOS score of the patient. Also, the nursing staff was already used to complete the DOS scale during routine care, so we did not need a run-in or training period for the study. In addition, during the conduct of the study the nurses gave very positive spontaneous feedback on the effort it took to complete this questionnaire.

There are several limitations to this study. First, the observed incidence of delirium at the study sites was low.[8] Therefore, it was necessary to adjust the results for non-verification. Even after this adjustment, we have convincing results that the DOS is an accurate screening instrument for

delirium screening in patients with advanced cancer. Second, while other baseline characteristics were evenly distributed over the DOS positive and DOS negative patients, patients who were DOS negative were younger than the DOS positive patients. This is concordant with the fact that advanced age is one of the known risk factors for the development of delirium.[2] Using age-matched comparators would however hamper the applicability of this study to the whole population of hospitalized patients with advanced cancer.

For this study we used a DRS-R-98 score of >17.75 as a cut-off for delirium. The patients who screened positive for delirium with the DOS scale but not with the DRS-R-98, had (except for one) DRS-R-98 scores >12, which has been classified as subsyndromal delirium in previous studies.[30,31] One might argue that it might be beneficial for these patients as well to be treated for their symptoms.

CONCLUSIONS

The DOS is an accurate instrument for detection of delirium in a population of hospitalized patients with advanced cancer. The DOS can be completed by nurses based on the observations made during regular nursing care, which makes it easily applicable as a screening tool for delirium in patients with advanced cancer. By early recognition and adequate treatment of this distressing delirium syndrome the quality of life of patients with advanced cancer can be improved.

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4

OLANZAPINE VS. HALOPERIDOL FOR TREATMENT OF DELIRIUM IN PATIENTS WITH ADVANCED CANCER – A PHASE III RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Background

Treatment of delirium often includes haloperidol. Second-generation antipsychotics like olanzapine have emerged as an alternative with possibly fewer side effects. The aim of this multicenter, phase III, randomized clinical trial (RCT) was to compare the efficacy and tolerability of olanzapine to haloperidol for the treatment of delirium in hospitalized patients with advanced cancer.

Patients and Methods

Eligible adult patients (≥18 years) with advanced cancer and delirium (Delirium Rating Scale-Revised-98 (DRS-R-98) total score ≥17.75) were randomized 1:1 to receive either haloperidol or olanzapine (age-adjusted, titratable doses). Primary endpoint was delirium response rate (DRR), defined as number of patients with DRS-R-98 severity score <15.25 and ≥4.5 points reduction. Secondary endpoints included time to recovery (TTR), tolerability, delirium-related distress.

Results

Between January 2011 and June 2016, 98 patients were included in the intention-to-treat analysis (ITT). DRR was 45% (95% confidence interval (CI): 31-59) for olanzapine and 57% (95% CI: 43-71) for haloperidol (Δ DRR -12%; odds ratio (OR): 0.61; 95% CI: 0.2-1.4; $p = 0.23$). Mean TTR was 4.5 days (95% CI: 3.2-5.9 days) for olanzapine, and 2.8 days (95% CI: 1.9-3.7 days; $p = 0.18$) for haloperidol. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 5 patients (10.2%), and in 10 patients (20.4%) in the olanzapine and haloperidol arm, respectively. Distress rates were similar in both groups. The study was terminated early because of futility.

Conclusion

Delirium treatment with olanzapine in hospitalized patients with advanced cancer did not result in improvement of DRR or TTR compared to haloperidol.

Clinical Trial Registration

ClinicalTrials.gov: NCT01539733. Dutch Trial Register: NTR2559.

INTRODUCTION

Delirium is a common, complex neuropsychiatric disorder with a high prevalence among hospitalized patients with advanced cancer.[1,2] This medical condition is characterized by changes in attention, awareness and cognition, which develop over a short period of time, and tend to fluctuate in severity during the course of a day.[3] Delirium is associated with high morbidity and also increased mortality;[4,5] it causes significant distress in patients and their caregivers, and interferes with symptom assessment and decision making.[6,7] Therefore, early recognition and adequate management of delirium is of utmost importance in the care of hospitalized patients with advanced cancer.

New guidelines recommend that the use of pharmacological interventions in the management of delirium should be limited to patients with distressing symptoms (such as agitation, anxiety, or perceptual disturbances), or if there are safety concerns where the patient is a potential risk to themselves or others.[8,9] In general, haloperidol, a typical or first-generation antipsychotic, is recommended as the first line pharmacological option.[10,11] A recently performed systematic review and meta-analysis of 15 randomized clinical trials suggested that atypical or second-generation antipsychotics, including olanzapine, have a benefit with regard to efficacy and safety compared to haloperidol.[12] Pooled atypical antipsychotics were associated with a shorter time to response (TTR) (Standard Mean Difference, SMD = -0.27) and a lower incidence (Risk Ratio, RR = 0.3) of extrapyramidal symptoms (EPS). However, most of the included studies were single center with small sample sizes, heterogeneous study populations, and at risk of bias.

Recently, a Cochrane systematic review included nine trials with 727 participants, assessing antipsychotics for delirium treatment in non-ICU patients.[9] Seven trials included a comparison of a typical to an atypical antipsychotic drug or placebo, including three studies, evaluating patients with advanced cancer.[13-15] Pooled analysis showed no significant difference in delirium severity (SMD -0.17, 95% CI: -0.4-0.02; seven studies; 542 participants), overall delirium resolution (RR 1.1, 95% CI: 0.8-1.5; five studies; 349 participants), overall mortality (RR 1.7, 95% CI: 0.8-3.5; four studies; 342 participants, or increased risk of EPS (RR 12.2, 95% CI: 0.55-270; two studies; 198 participants) with atypical antipsychotics compared to typical antipsychotics. There was no evidence to support or refute the suggestion that antipsychotics shorten the course of delirium in hospitalized patients. However, the results were assessed as (very) low evidence (downgraded due to risk of bias, inconsistency, and/or imprecision). Moreover, important clinical endpoints, like duration of delirium, health-related quality of life, and cardiac arrhythmia were not reported for any trial comparing typical vs. atypical antipsychotics.

Taken together, the efficacy and safety of pharmacological interventions for the treatment of delirium in patients with cancer is controversial. Effective and safe strategies for the management of delirium remain an unmet clinical need. Atypical antipsychotics may be an effective and safe alternative to haloperidol. Therefore, we conducted a multicenter, phase III RCT to compare the efficacy and tolerability of age-adjusted and titratable doses of olanzapine vs. haloperidol for the treatment of delirium in hospitalized patients with advanced cancer.

PATIENTS AND METHODS

Study design

This multicenter, randomized controlled, phase III trial (NCT01539733) was conducted at five sites (1 university cancer center, 2 teaching hospitals, 2 high-care hospices) in the Netherlands between January 2011 and July 2016. At the time of their admission, patients and/or their legal representatives were asked for written informed consent to participate in this study in case the patient was diagnosed with delirium during hospitalization. The method for concealment of allocation was by enclosing assignments in sequentially numbered, opaque, sealed envelopes provided by an independent third party (university medical center pharmacist). The envelopes were opened sequentially, and only after the envelope had been irreversibly assigned to the participant. The study staff assessing the effect of antipsychotic treatment was blinded to the participant's treatment group for the entire duration of the study. The clinical staff administering the study medication and the patient being treated, were not blinded. The study was conducted according to Good Clinical Practice guidelines, the Declaration of Helsinki and local laws, and was approved by the institutional review boards of each participating study site.

Patients

Eligible patients were ≥18 years of age with advanced cancer, who were admitted to a medical oncology ward or high-care hospice facility, who spoke the Dutch language fluently, and were diagnosed with delirium. Exclusion criteria included diagnosis of glaucoma, Parkinson's disease, dementia, psychiatric disorders interfering with delirium assessment, history of neuroleptic malignant syndrome or convulsions, delirium due to substance withdrawal, or cardiac conduction abnormalities (prolonged QTc interval of >500 msec on the electrocardiogram (ECG)). Patients being treated with other neuroleptic medication or lithium were also excluded from entering the study, because of the high probability of interactions (QTc prolongation, EPS, tardive dyskinesia, neuroleptic malignant syndrome etc.).

Procedures

Newly admitted patients were screened for delirium by the attending nurse using the Delirium Observation Scale (DOS) on set days (Mondays and Thursdays) during each nursing shift (day, evening, night), or whenever delirium was suspected by the nursing or medical staff. The DOS is a 13-item scale based on the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) criteria for delirium, designed to be completed by a nurse.[16] The DOS is an accurate screening scale for delirium in patients with advanced cancer.[17] The range of the total DOS score is 0-13; a total score of ≥3 indicates delirium. Patients with DOS score ≥3 were assessed on Delirium Rating Scale-R-98 (DRS-R-98) by a blinded assessor to confirm the diagnosis of delirium. The DRS-R-98 has 16 items, 13 of which assess the severity of symptoms, and 3 items are of diagnostic significance.[18] The rating is applicable to the preceding 24h. Each severity item's rating levels are anchored with descriptions appropriate to that particular symptom. The severity ratings range from 0 (no impairment) to 3 (severe impairment), and a severity score of ≥15.25, or a total

score of ≥17.75 is indicative of delirium; higher scores indicate higher severity of delirium. Delirium is considered cleared, if the severity score is <15.25 with a decline of at least 4.5 points (d = 0.8) in the total score.[18] Site initiation involved training of the clinical and study staff for standardized assessment of DOS and DRS-R-98 scores (performed by MV and EN).

Once delirium was diagnosed, potential precipitating factors for delirium, including changes in dose or type of opioids (<48 hours before diagnosis of delirium), dehydration, infection, intracranial malignancy, infection, and metabolic imbalances were identified and scored (yes or no) by a comprehensive assessment. Delirium was categorized according to motor subtype (hypoactive, hyperactive or mixed), based on DRS-R-98 items 7 (motor agitation) and item 8 (motor retardation). We also determined the predominance of certain "psychomotor features" by clinical observation. The hypoactive subtype is characterized by reduced alertness, sedation, and reduction of motor activity. The hyperactive form is associated with hyper vigilance, overt psychotic features (e.g., hallucinations, delusions), and agitation. The mixed subtype has overlapping features of the hypoactive and hyperactive subtypes. All patients received tailored interventions targeted at the underlying causes of delirium, and appropriate non-pharmacological measures were taken according to clinical practice guidelines.[8,10,11] Subsequently, all patients were randomized in a 1:1 ratio to receive haloperidol orally (PO) or subcutaneously (SC), or olanzapine PO or intramuscularly (IM). Dosing of antipsychotics was age-adjusted and based on clinical practice guidelines.[10,11]

Patients <75 years of age assigned to haloperidol started with a loading dose of 1 mg. DOS scores were determined every 40 minutes thereafter. If the DOS score was ≥3, subsequent doses were increased by 1 mg up to a maximum dose of 20 mg PO or 10 mg SC on day 1 (Supplementary Table 1). Patients <75 years of age assigned to olanzapine started with a loading dose of 5 mg. DOS scores were determined every 2 h thereafter. If the DOS score was ≥3, subsequent doses were increased to a maximum dose of 20 mg PO or IM (Supplementary table 2). The loading, titration, and maximum doses of both haloperidol and olanzapine were halved for patients ≥75 years of age.

If the DOS score was <3, resolution of delirium was confirmed by DRS-R-98 assessment. Maintenance dose of haloperidol or olanzapine was one half of the total dose of the study drug administered during the first 24 h after initiation, and divided in 1 or 2 doses. On days 2, 3, 4 and 7, DRS-R-98 assessment was repeated. If the DRS-R-98 severity score was ≥15.25, maintenance doses of haloperidol and olanzapine were adjusted (Supplementary Table 1 and 2).

Treatment with antipsychotics was discontinued if the maximum daily dose of the study drug was reached without resolution of delirium, or if serious (grade ≥3) treatment-related adverse events (TRAEs) occurred. TRAEs, including somnolence, dizziness, and EPS (including tremors and muscle stiffness) were monitored and graded daily according to the *Common Terminology Criteria for Adverse Events* (CTCAE) version 4.03[19] by the study staff. ECG was performed before initiation of the study drug, and on day 2. If QTc prolongation (>500msec) occurred, treatment with the study drug was also discontinued. Administration of the benzodiazepine receptor agonist lorazepam PO or intravenously (IV) was allowed, if the patient was deemed to require immediate intervention for safety or distress by the clinical staff. There was no pre-determined dose schedule for the administration of PO or IV lorazepam. For optimal results, dose, frequency of administration, and duration of therapy with lorazepam was individualized according to patient response.

Patients who had recovered from delirium were asked to complete the Delirium Experience Questionnaire (DEQ). The DEQ is a face-valid brief questionnaire asking six questions (three questions, yes/no; two questions, 0–4 numerical rating scale (NRS) with 0 = at all and 4 = extremely; one question, qualitative assessment) to assess recall of the delirium experience and the degree of distress related to the delirium episode.[6] Spouse/caregivers and attending nurses were also asked to complete the DEQ to assess the level of caregiver distress.

Endpoint and statistical analysis

The primary endpoint was delirium response rate (DRR) on days 1-7 after randomization as defined by DRS-R-98 assessment (severity score <15.25; decline ≥ 4.5 points total score). Secondary endpoints included: time to recovery (TTR), defined as the time from randomization to resolution of delirium (number of days); TRAEs according to CTCAE version 4.03; delirium-related distress for patients and their caregivers assessed by DEQ. An exploratory analysis of DRR was conducted for each motor subtype of delirium.

Assuming a 25% improvement in DRR (from 50% to 75%) with olanzapine compared to haloperidol[20] with alpha set to 5% and power to 90%, and an expected dropout rate of 15%, the total sample size was 100 evaluable patients per treatment arm. DRR was compared between the two randomized groups by chi-square tests, and by calculating the 95% confidence interval (CI) of the difference of the proportions in both the intention-to-treat (ITT) and the per protocol (PP) cohort (i.e. all patients who completed antipsychotic treatment). TTR outcomes in the ITT cohort were compared between the two treatment groups in the ITT by using stratified log-rank tests and were plotted in a Kaplan-Meier curve. TRAEs and DEQ scores were analyzed in an explorative or descriptive manner. All reported *p*-values are two-sided.

Futility analysis was conducted after 50% (n = 100) of the patients required for DRR analysis was included. The threshold for futility was set at a conditional power of 10%, which is usually applied as a stopping rule.[21] All analyses were conducted by an independent statistician using IBM SPSS statistics version 22 (Chicago, IL, United States).

RESULTS

Between January 1, 2011 and June 15, 2016, a total of 100 patients were randomly assigned: 50 patients per treatment arm (Figure 1). Data were missing from one patient in each treatment arm. Ninety-eight patients (49 patients per treatment arm) were included in the ITT cohort; 81 patients (40 in the olanzapine arm, and 41 in the haloperidol arm) in the PP cohort.

Table 1 describes the baseline characteristics of the ITT population, which were generally well balanced between the two arms. The majority of the patients was male (69.4%) with a mean age of ±69 years in both treatment groups. Mean DRS-R-98 total score at randomization was approximately 23 in both arms. Median number of precipitating factors for delirium was 2 (Interquartile Range, IQR, 1-3; Range, 0-5). Most patients (n= 89; 91%) were admitted to a hospital ward. Reason for hospitalization was an emergency admission in 84.7% of the patients.

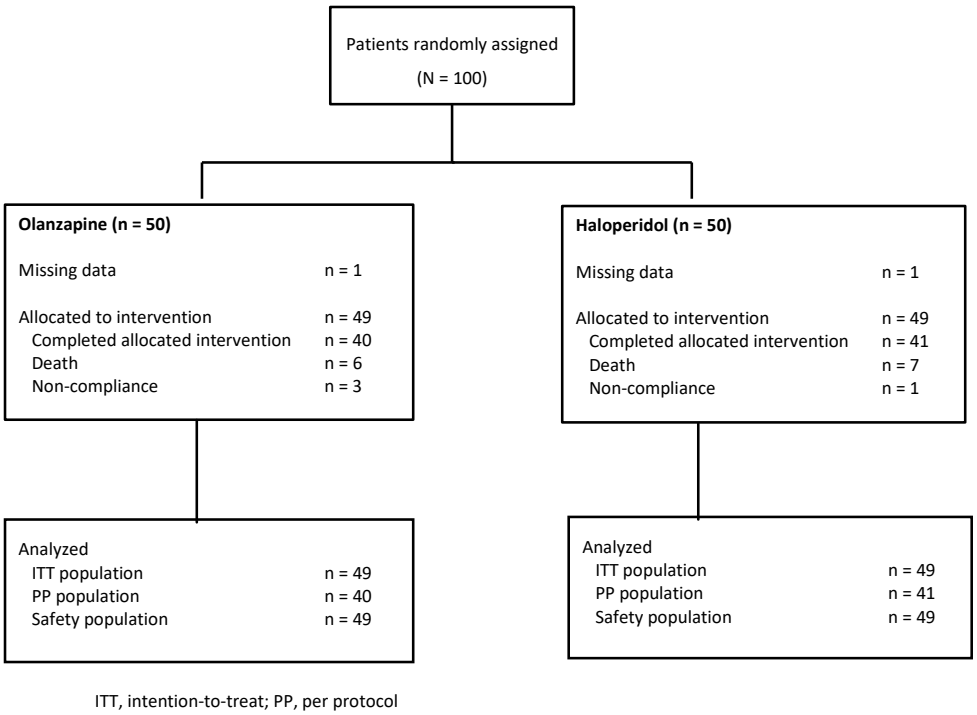

Figure 1. CONSORT diagram.

Efficacy

On day 1, median olanzapine dose was 8.8 mg (IQR, 5.0-15.0 mg), 5.0 mg (IQR, 0.0-10.0 mg) on day 2, and 5.0 mg (IQR, 1.9-10.0 mg) at the end of study. For haloperidol, median dose was 2.5 mg (IQR, 1.0-4.8 mg) on day 1, 1.3 mg (IQR, 0.5-2.9 mg) on day 2, and 1.8 mg (IQR, 0.5-2.8 mg) at the end of study.

In the ITT cohort, DRR was 45% (95% CI: 31-59) for olanzapine, and 57% (95% CI: 43-71) for haloperidol (Δ DRR -12%; odds ratio (OR) = 0.61 [95% CI: 0.2-1.4]; p= 0.23). DRR was 56% for olanzapine (95% CI: 41-72), and 68% (95% CI 54-83) for haloperidol (Δ DRR -12%; OR = 0.61 [95% CI: 0.2-1.5]; p= 0.27) in the PP cohort. Mean TTR in the olanzapine arm was 4.5 days (95% CI: 3.2-5.9), and 2.8 days (95% CI: 1.9-3.7; p= 0.18) in the haloperidol arm. (Figure 2). Exploratory analysis did not demonstrate any significant benefit of olanzapine in DRR for hyperactive, hypoactive, or mixed subtypes (Table 2).

Futility analysis was conducted, and at this time, the conditional power was 8.6%. As the conditional power was lower than the threshold for futility, this analysis indicated that this study was unlikely to reach the predefined efficacy criteria. Therefore, recruitment was terminated prematurely (June 15, 2016).

Table 1. Baseline characteristics of patients

	Olanzapine (*N* = 49)	Haloperidol (*N* = 49)
Mean age, years (SD)	69.9 (9.3)	68.4 (11.9)
Sex, No. (%)		
Male	33 (67)	35 (71)
Female	16 (33)	14 (29)
DRS-R-98[1]		
Severity score, mean (SD)	18.1 (3.8)	17.6 (3.4)
Total score, mean (SD)	23.5 (3.9)	23.1 (3.4)
Delirium subtype, No. (%)		
Hyperactive	16 (33)	20 (41)
Hypoactive	10 (20)	17 (35)
Mixed	21 (43)	12 (24)
Unspecified	2 (4)	-
Use of opioids, No. (%)	33 (67)	35 (71)
Use of benzodiazepines, No. (%)	18 (37)	21 (43)
Use of neuropathic pain medication, No. (%)	7 (14)	11 (22)
Use of psychotropic medication, No. (%)	3 (6)	4 (8)
Precipitating factors[2],	2 (1-3; 0-5)	2 (1-3; 0-5)
Median No. (IQR[3]; range)		
Admission type, No. (%)		
Hospital	45 (92)	43 (88)
Hospice	4 (8)	6 (12)
Reason for admission, No. (%)		
Emergency	41 (84)	42 (86)
Scheduled	8 (16)	7 (14)

[1] Delirium Rating Scale-Revised-98

[2] Precipitating factors included: change in dose or type of opioids (<48 hours before diagnosis of delirium); dehydration; infection; intracranial malignancy; infection; metabolic imbalances

[3] Interquartile range

Safety

TRAEs were in line with previous data,[9] with TRAEs of any grade occurring in 13 patients (26.5%) in the olanzapine arm, and 16 patients (32.7%) in the haloperidol arm (Table 3). Grade ≥3 TRAEs (all leading to drug discontinuation) were reported in 5 patients (10.2%) in the olanzapine arm, and 10 patients (20.4%) in the haloperidol arm (OR= 0.4; 95% CI: 0.1-1.4; *p*= 0.16). Sedation was the most reported grade ≥3 TRAE, in 5 (10.2%) and 7 (14.3%) patients in the olanzapine and haloperidol arms, respectively. Grade ≥3 EPS (including tremors and muscle stiffness) occurred in two patients in the haloperidol arm; there was no reported grade ≥3 EPS in the olanzapine arm. One patient in the haloperidol arm experienced QTc prolongation (>500msec), and none in the olanzapine arm. All grade ≥3 TRAEs occurred on day 1 or 2. There were no treatment-related deaths in both treatment arms.

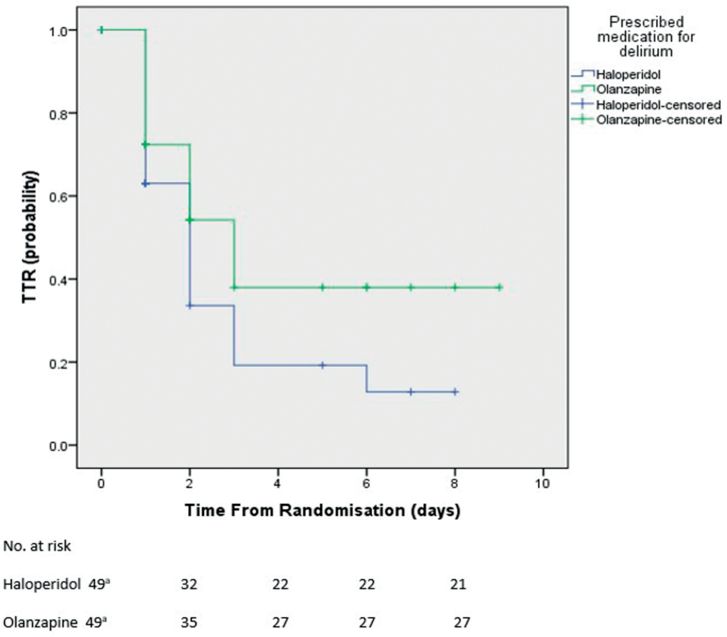

Figure 2. Kaplan-Meier estimates of time to response (TTR) according to treatment arm

Table 2. Subgroup analysis by delirium motoric subtype of the delirium resolution rate in the intention-to-treat cohort.

Delirium resolution rate			
Motoric subtype	**Olanzapine (N (%))**	**Haloperidol (N (%))**	**OR, 95% CI (P value*)**
Hyperactive	8/16 (50)	13/20 (65)	0.54, 0.14-2.06 (0.50)
Hypoactive	3/10 (30)	11/17 (65)	0.23, 0.04-1.53 (0.12)
Mixed	10/21 (47)	4/12 (33)	1.82, 0.42-7.94 (0.49)

* P two-sided chi-square test (olanzapine vs. haloperidol)

Delirium-related distress

Sixteen patients in each treatment arm completed the DEQ. Mean delirium-related distress level (on a 0-4 numerical rating scale) was 2.1 (Standard Deviation, SD 1.4) in the olanzapine arm, and 2.3 (SD 1.4) in the haloperidol arm. The mean delirium-related distress level rated by spouses/caregivers was 2.7 (SD 1.1) in the haloperidol arm, and 3.0 (SD 1.2) in the olanzapine arm. Mean delirium-related distress level rated by attending nurses was 0.9 (SD 0.9) in the haloperidol arm, and 1.1 (SD 1.1) in the olanzapine arm.

Table 3. Incidence of TRAEs in the safety analysis set

	Haloperidol (n = 49)			Olanzapine (n = 49)		
	Any grade	Grade 3	Grade 4/5	Any grade	Grade 3	Grade 4/5[a]
Any TRAE	16 (32.7)	10 (20.4)	0	13 (26.5)	4 (8.2)	1 (2.0)
Sedation	10 (20.4)	7 (14.3)	0	9 (18.4)	4 (8.2)	1 (2.0)
Tremor	3 (6.1)	1 (2.0)	0	2 (4.1)	0	0
Muscle stiffness	2 (4.1)	1 (2.0)	0	1 (2.0)	0	0
Dizziness	0	0	0	1 (2.0)	0	0
QTc prolongation	1 (2.0)	1 (2.0)	0	0	0	0

Data are number of patients (%).
The safety analysis set comprised all patients who were administered any dose of the study medication.
[a]All TRAEs with olanzapine were grade 4.

DISCUSSION

This multicenter, phase III RCT demonstrated no statistically significant difference in efficacy between olanzapine and haloperidol for the treatment of delirium in hospitalized adult patients with advanced cancer. Treatment with olanzapine did not result in a better DRR or shorter TTR compared to haloperidol. This trial met criteria for early stopping due to futility.

The management of delirium is complex because of the considerable heterogeneity in terms of etiology and clinical subtype.[22,23] A number of brain neural networks and pathways have been implicated, but underlying pathophysiological mechanisms remain poorly understood.[24,25] The complexity of delirium suggests that a variety of interventions is most likely needed, which combines both non-pharmacological and pharmacological strategies, as appropriate to the cancer trajectory and goals of care. The question remains whether antipsychotic drugs are clinically useful and safe for the treatment of delirium in patients with advanced cancer. If so, are atypical antipsychotics preferred because of their possibly better adverse effect profile and efficacy advantages in some patients?

Collective data remains limited on the activity and safety of antipsychotic drugs for the treatment of delirium in patients with advanced cancer. A recently performed Cochrane review on antipsychotics for treatment of delirium in hospitalized non-ICU patients[9] included three studies comparing typical to atypical antipsychotics for the treatment of delirium in patients with advanced cancer.[13-15] Lin et al (n= 30; 100% with a cancer diagnosis) performed a single-center, open RCT, and compared the efficacy between haloperidol and olanzapine to treat delirium (DSM-IV criteria) in palliative and hospice center cancer patients. Comparison of the scores of Delirium Rating Scale-Chinese (DRS-c) and Clinical Global Impression-Severity (CGI-S) between two groups showed no statistical difference. The study by Maneeton et al (n= 52; 38.5% with cancer diagnosis) was a single-center, prospective, double-blind RCT which compared quetiapine vs. haloperidol for the treatment of delirium (DSM-IV-TR and Confusion Assessment Method (CAM) criteria). The primary outcome measure was the DRS-R-98. They concluded that low-dose quetiapine and haloperidol were equally effective and safe.

The 2018 ESMO clinical practice guideline on delirium in adult cancer patients[8] identified 15 studies, including three RCT's.[15,26,27] Kim et al (n=32; 72% with a cancer diagnosis) compared risperidone with olanzapine over a 7-day period.[26] The primary outcome measure was the DRS-R-98. There was no significant difference in either efficacy or adverse effects in this underpowered study. The second study by Hui et al (n= 90; 100% with a cancer diagnosis) was a single-center, double-blind, parallel group RCT conducted in adult patients with advanced cancer, comparing the effect of lorazepam vs. placebo as an adjuvant to haloperidol for persistent agitation (RASS score of ≥ +2) in patients with delirium (DSM-IV-TR criteria).[27] This study was designed to assess a different primary research objective than our RCT.

Recently, Agar et al[15] conducted a three-armed, multicenter, placebo-controlled study of antipsychotic treatment of delirium in patients receiving palliative care (n = 247, 88% with a cancer diagnosis). Treatment with either risperidone or haloperidol was associated with significantly greater delirium symptom severity scores and mean extrapyramidal effects than placebo. There was no comparison of haloperidol vs. risperidone in the Agar study. As a secondary outcome, haloperidol treatment was associated with poorer overall survival in long-term follow-up. However, there are some considerations that need to be addressed. First, although the therapeutic dose of haloperidol and the optimal dose titration schedule for delirium remain to be defined, starting and maintenance doses of haloperidol for patients >65 years of age (0.25 mg PO bid, increased to a maximum of 2 mg/day) used in the Agar study were low compared with doses reported in previous studies in the oncology/palliative care setting.[28] This may have underestimated the clinical effect of antipsychotic drugs to treat delirium in patients with advanced cancer. Furthermore, differences at baseline between the haloperidol and placebo arms in number of patients aged >65 years (90% vs. 80%, respectively), and the median dose of opioids (33 vs. 15 mg, respectively), are factors that may have affected study results. Other possible factors impacting on study results in the Agar study are older age and dementia/cognitive impairment, which are predictors of poor response to antipsychotics in the treatment of delirium.[20,29-32] In the study by Agar et al, mean age of the patients in the haloperidol arm was 76.5 years (21% diagnosed with cognitive impairment), and in the risperidone arm mean age was 74.5 years (22% with cognitive impairment). Median IQCODE (a structured questionnaire to detect individuals who may go on to develop dementia) scores for cognitive impairment were ≥4, which shows that long-term decline of cognitive status was highly prevalent. In our study, mean age was <70 years in both treatment arms, and patients with dementia were excluded. To conclude, prescribing of antipsychotic drugs for patients with delirium remains a matter of debate.[33] Future studies need to identify baseline factors indicating which patients will benefit most from upfront treatment with antipsychotic drugs.

Overall, the safety profiles of haloperidol and olanzapine in the dose range tested were in line with previous studies in non-ICU patients with delirium.[9] TRAEs of any grade occurred in 32.7% and 26.5% of the patients in the haloperidol and olanzapine arm, respectively. TRAEs grade ≥3 (all leading to drug discontinuation) were reported more frequently in the haloperidol arm: 20.4 % vs. 10.2% in the olanzapine arm; however, this difference was not statistically significant. The most common grade ≥3 TRAE was sedation in both treatment arms. EPS grade ≥3 was uncommon, occurring in 4% of the patients in the haloperidol arm. Only three patients in the olanzapine arm

experienced low grade EPS; EPS grade ≥3 did not occur in the olanzapine arm. All TRAEs resolved without sequelae when the study drug was discontinued. The use of antipsychotics is associated with QTc prolongation, which can lead to life-threatening arrhythmia.[34-36] In this study with routine ECG assessment only one atrioventricular block episode was reported in the haloperidol arm.

Previous reports indicate high levels of delirium-related distress in patients and their caregivers.[5-7] In our study, exploratory analysis showed that mean stress scores reported by patients were just above 2 (on a 4 point rating scale) in both treatment arms. As expected, stress scores reported by spouses and care-givers were high: 2.7 vs. 3.0 in the haloperidol and olanzapine arm, respectively. Scores reported by attending nurses were low in both treatment arms. This could be the effect of improved professional education, providing nurses with educational resources and opportunities to apply knowledge with regard to delirium, which increases confidence in identification and management of delirium.[37,38]

This study has some limitations. First, our study did not include a placebo control group. The absence of a comparative placebo control group with active treatment groups limits the interpretation of our findings. Second, the DOS was completed not on a daily basis, but at fixed times twice-weekly, or whenever delirium was suspected. Daily assessments were not feasible given the high workload of the nursing staff. Consequently, some delirious cases may have remained undetected. Third, although the rater of the DRS-R-98 scores was blinded to the study drug, as the rater knew that all subjects were receiving active treatment, DRS-R-98 ratings could have been affected. Fourth, non-pharmacological interventions for the prevention and treatment of delirium were not standardized across the participating 5 sites in this study. However, it should be noted that for most non-pharmacological interventions, there is limited research evidence on which to base clinical recommendations. Interventions based on the Hospital Elder Life Program (HELP)[39] have been successfully implemented in all Dutch healthcare institutions. Fifth, the decision of stopping this trial early for futility was adopted as a consequence of the results of the interim analysis, which demonstrated that it was highly unlikely that the trial would meet its primary objective of demonstrating superiority of olanzapine over haloperidol. With a probability rate of 8.6% to achieve its primary objective, this was well below the threshold of 10% for futility. Consequently, the number of included patients is relatively small, and the power of the analyses performed to assess secondary endpoints is low. Finally, the use of rescue interventions to manage agitation (e.g. benzodiazepines and physical restraints) were not prospectively recorded. Because these interventions are known to be associated with delirium, this could have introduced bias. However, it should be noted that retrospective analysis of the medical records showed that only very few patients (<3%) received benzodiazepines, and none physical restraints.

In conclusion, the atypical antipsychotic olanzapine and haloperidol were equally effective and safe for the management of delirium in a broad population of hospitalized patients with advanced cancer. The focus of future placebo-controlled RCT's should change to individualized, multimodal intervention strategies for managing delirium.

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SUPPLEMENTARY DATA

Supplementary Table 1

DOSE ADJUSTMENT ALGORITHM FOR HALOPERIDOL

On day 1, haloperidol dosing was increased according to standard guidelines with repeating dosing of 1.0 mg every 40 minutes until delirium resolved. Maximum dose allowed was 20 mg orally or 10 mg subcutaneously per 24 hours. The loading, titration, and maximum dose of haloperidol was halved for patients ≥75 years of age.

Maintenance dose on day 2 was one half of the total dose of haloperidol administered during the first 24 hours, which was divided in 1 or 2 doses. The maintenance dose of haloperidol was halved for patients ≥75 years of age.

Haloperidol	Day 2: maintenance dose			
Total dose (mg) day 1*	Evening dose (mg)	Morning dose (mg)	Rescue dose (mg; maximum twice daily)	Total dose (mg) day 2
1	0,5	0	0,5	1,5
2	0,5	0,5	0,5	2
3	1	0,5	0,5	2,5
4	1	1	1	4
5	1,5	1	1	4,5
6	1,5	1,5	1,5	6
7	2	1,5	1,5	6,5
8	2	2	2	8
9	2,5	2	2	8,5
10	2,5	2,5	2,5	10
11	3	2,5	2,5	10,5
12	3	3	3	12
13	3,5	3	3	12,5
14	3,5	3,5	3,5	14
15	4	3,5	3,5	14,5
16	4	4	4	16
17	4,5	4	4	16,5
18	4,5	4,5	4,5	18
19	5	4,5	4,5	18,5
20	5	5	5	20

*Total dose ended .5 are rounded up

**With maximum use of rescue dose

On day 2, delirium assessment with DRS-R-98 is repeated. Resolution of delirium was defined as a DRS-R-98 total severity score of < 15.25 points with a ≥ 4.5 points reduction in the severity items scores.

If on day 3 the severity score of DRS-R-98 is ≥ 15.25 points, maintenance dose of haloperidol is increased according to the following guideline.

Haloperidol	Day 3: maintenance dose			
Total dose (mg) day 2*	Evening dose (mg)	Morning dose (mg)	Rescue dose (mg; maximum twice daily)	Total dose (mg) day 3**
1,5	1	1	1	4
2	2	1	1	5
2,5	2	2	2	8
4	2,5	2,5	2	9
4,5	3	3	2	10
6	4	4	2	12
6,5	4	4	2	12
8	5	5	2,5	15
8,5	5	5	2,5	15
10	6	6	3	18
10,5	6	6	3	18
12	7	7	3	20
12,5	7	7	3	20
14	7,5	7,5	2,5	20
14,5	7,5	7,5	2,5	20
16	8	8	2	20
16,5	8,5	8,5	1,5	20
18	9	9	1	20
18,5	9,5	9,5	0,5	20
20	10	10	0	20

*Total dose ended .5 are rounded up

**With maximum use of rescue dose

On day 4, delirium assessment with DRS-R-98 is repeated. Resolution of delirium was defined as a DRS-R-98 total severity score of < 15.25 points with a ≥ 4.5 points reduction in the severity items scores.

If on day 4 the severity score of DRS-R-98 is ≥ 15.25 points, maintenance dose of haloperidol is increased according to the following guideline.

Haloperidol	Day 4: maintenance dose#			
Total dose (mg) day 3*	Evening dose (mg)	Morning dose (mg)	Rescue dose (mg; maximum twice daily)	Total dose (mg) day 4**
4	2.5	2.5	2	9
5	3	3	2	10
8	5	5	2.5	15
9	5	5	2.5	15
10	6	6	3	18
12	7	7	3	20
15	8	8	2	20
18	9	9	1	20
20	10	10	0	20

Day 4 and following days

* Total dose ended .5 are rounded up

**With maximum use of rescue dose

On days 7 and 14, delirium assessment with DRS-R-98 is repeated. Resolution of delirium was defined as a DRS-R-98 total severity score of < 15.25 points with a ≥ 4.5 points reduction in the severity items scores.

Supplementary Table 2

DOSE ADJUSTMENT ALGORITHM FOR OLANZAPINE

On day 1, olanzapine was increased with repeating dosing of 5.0 mg every 2 hours until delirium resolved. Maximum dose allowed was 20 mg (both orally and intramuscularly) per 24 hours. Maintenance dose was one half of the total dose of olanzapine administered during the first 24 hours, which was divided in 1 or 2 doses. The loading, titration, maintenance, and maximum dose of olanzapine was halved for patients ≥75 years of age.

Maintenance dose on day 2 was one half of the total dose of olanzapine administered during the first 24 hours, which was divided in 1 or 2 doses.

Olanzapine	Day 2: maintenance dose			
Total dose (mg) day 1	Evening dose (mg)	Morning dose (mg)	Rescue dose (mg; maximum once daily)	Total dose (mg) day 2*
2.5	2.5	0	2.5	5
5	2.5	0	2.5	5
7.5	2.5	2.5	2.5	7.5
10	2.5	2.5	2.5	7.5
15	5	2.5	2.5	10
20	5	5	5	15

*With maximum use of rescue dose

On day 2, delirium assessment with DRS-R-98 is repeated. Resolution of delirium was defined as a DRS-R-98 total severity score of < 15.25 points with a ≥ 4.5 points reduction in the severity items scores.

If on day 3 the severity score of DRS-R-98 is ≥ 15.25 points, maintenance dose of haloperidol is increased according to the following guideline.

Olanzapine	Day 3: maintenance dose			
Total dose (mg) day 2	Evening dose (mg)	Morning dose (mg)	Rescue dose (mg; maximum once daily)	Total dose (mg) day 3*
5	5	2.5	2.5	10
7.5	5	5	2.5	12.5
10	7.5	5	5	12.5
15	10	7.5	2.5	20

*With maximum use of rescue dose

On day 4, delirium assessment with DRS-R-98 is repeated. Resolution of delirium was defined as a DRS-R-98 total severity score of < 15.25 points with a ≥ 4.5 points reduction in the severity items scores.

If on day 4 the severity score of DRS-R-98 is ≥ 15.25 points, maintenance dose of haloperidol is increased according to the following guideline.

Olanzapine	**Day 4: maintenance dose***			
Total dose (mg) day 3	**Evening dose (mg)**	**Morning dose (mg)**	**Rescue dose (mg; maximum once daily)**	**Total dose (mg) day 4****
10	7.5	5	5	17.5
12.5	7.5	7.5	5	20
17.5	10	10	0	20
20	10	10	0	20

*Day 4 and following days

**With maximum use of rescue dose

On days 7 and 14, delirium assessment with DRS-R-98 is repeated. Resolution of delirium was defined as a DRS-R-98 total severity score of < 15.25 points with a ≥ 4.5 points reduction in the severity items scores.

5

CLINICAL EVALUATION OF THE EFFICACY OF METHYLNALTREXONE IN RESOLVING CONSTIPATION INDUCED BY DIFFERENT OPIOID SUBTYPES COMBINED WITH LABORATORY ANALYSIS OF IMMUNOMODULATORY AND ANTIANGIOGENIC EFFECTS OF METHYLNALTREXONE

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ABSTRACT

Background

Opioid-induced constipation (OIC) is one of the major symptoms in palliative care with a prevalence of 30-50%. Methylnaltrexone for the treatment of OIC is significantly more effective than placebo, but only in about fifty percent of the patients regardless of dose increase. Dose increases cause increased toxicity without additional efficacy, and are therefore not recommended. While methylnaltrexone is a μ-receptor antagonist, only a few opioids are solely μ-receptor agonists. Therefore, the response to methylnaltrexone may be determined by the receptor-profile of a specific opioid. In addition, methylnaltrexone may also affect the immune system and angiogenesis as was found in pre-clinical studies. Primary aim of this study is to determine differences in the efficacy of methylnaltrexone prescribed to resolve opioid induced constipation between three commonly used opioid subtypes: morphine sulphate, oxycodone and fentanyl. Secondary aim is to explore potential immunomodulatory and antiangiogenic effects of methylnaltrexone.

Methods

In this multi-center, prospective, parallel group trial we will evaluate the efficacy of methylnaltrexone in resolving OIC occurring as a side effect of the most common opioid subtypes: morphine, oxycodone and fentanyl. In total 195 patients with OIC despite prophylactic laxatives will receive methylnaltrexone every other day up to fourteen days. Patients will report its effect in a laxation diary. Group allocation is based on the opioid type the patient is using. At the start and end of the study period patients complete the Bowel Function Index questionnaire. A subgroup of the patients will donate blood for analysis of immunomodulatory- and anti-angiogenic effects of methylnaltrexone.

Discussion

In this study we aim to determine the efficacy of methylnaltrexone per opioid subtype to reduce constipation. We expect that the outcome of this study will improve the clinical use of methylnaltrexone.

Trial registration

This trial is registered at clinicaltrials.gov: NCT01955213 and in the Dutch trial register: NTR4272.

BACKGROUND

Constipation is one of the major symptoms in palliative care, with a prevalence rate of 30-50% in patients with cancer.[1,2] It leads to a noticeable decrease in quality of life[3] by causing physical symptoms such as bloating and straining, and sometimes necessitates hospitalization.[4] Constipation can have multiple causes, which can be divided into anorectal dysfunction, or slow colon transit.[5] In palliative care for patients with cancer mechanical obstruction by tumor depositions or ascites might also be a cause of constipation, but often constipation is caused by opioid use. The incidence of opioid induced constipation (OIC) is estimated to vary between 35 and 70% of the patients using opioids.[4,6-8] This large range is probably caused by variation in type and dosage of opioids, the amount of (prophylactic) laxatives used and the way patients are monitored for this side effect in different studies.[4,6-8] The Rome criteria (currently version III) are generally used to diagnose constipation.[5] According to the Rome III criteria for constipation, a patient must have experienced at least 2 of the following symptoms over the preceding 3 months with symptom onset at least 6 months before diagnosis: fewer than 3 bowel movements per week, straining, lumpy or hard stools, sensation of anorectal obstruction, sensation of incomplete defecation, and/or manual maneuvering required to defecate. However, these diagnostic criteria might not be applicable to patients with OIC, because they require the presence of complaints for at least six months, while OIC usually develops within days to weeks and might need urgent treatment. Therefore, a practical definition of OIC is a decrease of the frequency of bowel movements after initiation of opioids to a frequency of less than three bowel movements per week.[9] To prevent OIC, guidelines recommend prophylactic laxatives.[10,11] Most patients are able to manage their bowel movements by in- or decreasing the dosage of the laxatives they use. However, 12-20% of the patients report symptoms of OIC despite laxative prescription.[12] For these patients methylnaltrexone, a peripherally acting μ-opioid receptor antagonist, can be a valuable therapeutic option.

Opioids exert their action through the opioid-receptors. These receptors are present in the central nervous system but also in peripheral tissues. Under normal conditions opioid receptors are receptive to endogenous opioids, such as enkephalins and endorphins.[13] The three major types of opioid receptors are the mu (μ), kappa (κ) and delta (δ) opioid receptor.[13] The affinity for the different receptors varies between different types of opioids.[13] How each receptor type contributes to OIC is not fully understood. There is evidence that each receptor type has an effect on gastro-intestinal motility and fluid secretion.[14] Previous studies suggest that these effects are mainly mediated by the peripheral opioid receptors.[14-16]

Methylnaltrexone

Methylnaltrexone (Relistor®) is an opioid receptor antagonist which blocks opioid binding at the μ-receptor but also has some affinity for the κ-receptor. It is a quaternary derivative of naltrexone with restricted ability to cross the blood–brain barrier. It therefore functions as a peripherally acting opioid antagonist, which reduces the opioid-induced decrease in gastrointestinal motility and delay in gastrointestinal transit time, and thereby reduces OIC. Methylnaltrexone does not affect opioid analgesic effects or induce opioid withdrawal symptoms. It is excreted by the kidneys

and in the feces and has a plasma half-life of approximately 8 hours. The most common side effects of methylnaltrexone are abdominal pain, nausea, flatulence, and diarrhea, which are likely to be related to increased peristaltic activity.[17] Methylnaltrexone has been approved by the FDA and EMA for patients who receive palliative care (regardless of medical condition) with OIC despite prophylactic laxative use.

Methylnaltrexone for the treatment of OIC is significantly more effective than placebo.[9] However, in both the randomized and open-label phases of the pivotal multi-center trial, methylnaltrexone produced rescue-free laxation in only about half the patients.[9] Dose increases did not influence these results.[18] There may be several reasons for this observation. First, constipation in palliative care patients may have multiple simultaneously occurring causes, unrelated to opioid therapy. Second, assuming that the constipation of the non-responders is still opioid-induced, one can hypothesize that the response to methylnaltrexone could be determined by the receptor-profile of the specific opioid the patient is using (Table 1).[4,6-8,19] This is because methylnaltrexone is primarily a μ-receptor antagonist, while not all opioids are solely μ-receptor agonists. A frequently prescribed opioid like oxycodone is a κ-receptor and δ-receptor agonist[13] as well as μ-receptor agonist, whereas morphine and fentanyl are both mainly μ-receptor agonists. Morphine and fentanyl, on the other hand, differ in their lipid solubility and their tendency to sequestrate in the central nervous system.[13] This may possibly contribute to differences in response to methylnaltrexone, because methylnaltrexone is unable to pass the blood–brain barrier.

In all previously mentioned studies no comparison was made between the response rates to methylnaltrexone of patients using different types of opioids[9,17] Therefore, we recently initiated a clinical trial to determine whether different receptor-profiles of opioids are related to the efficacy of methylnaltrexone.

Besides constipation, there are other side effects of opioids that might be of clinical importance. Acute and chronic use of opioids is known to have inhibitory effects on humoral and cellular immune responses and may also have a stimulating effect on angiogenesis.[20-24] Mu-type opioid receptors are identified in several immunological cell subsets,[25,26] and it has been demonstrated that opioids suppress T cell functioning and the production of several cytokines.[23,27-29] Activation of the μ-opioid receptor expressed on endothelial cells stimulates angiogenesis and a synergistic effect of morphine sulphate with VEGF has been demonstrated.[21,30,31] Methylnaltrexone could be of additive value to prevent this unwanted immunomodulatory and angiogenic activity of opioids.[30] Therefore, we will study the effects of methylnaltrexone on immunomodulatory and angiogenic activity in patients during treatment with this agent.

Aims

Primary aim of the study is to compare the efficacy of a fixed dose of subcutaneous methylnaltrexone to induce laxation in patients who suffer from constipation due to either fentanyl, oxycodone or morphine sulphate despite optimal prophylactic laxative use.

Secondary aims are 1) to determine size, phenotype, and function of various leukocyte subsets as well as serum cytokine levels during treatment with the μ-opioid receptor antagonist

Table 1. Opioid characteristics regarding constipation

Opioid	Receptor affinity	Lipophilicity	Distribution site	Incidence of constipation[1]
Morphine Sulphate	Mainly μ, some κ	Low	Peripheral	60% (range 21-70%)
Oxycodone	μ, κ and δ	Intermediate	Central and peripheral	65% (range 25-74%)
Fentanyl	μ (highly selective)	high	Central	35% (range 10-55%)

[1] Estimated incidence of constipation without laxative use and the range of this incidence found in different studies in which a proportion of patients already uses laxatives.

methylnaltrexone and 2) to determine whether systemic antagonistic treatment with methylnaltrexone will modify systemic biomarkers of angiogenesis.

METHODS

This study is a multi-center, prospective, parallel-group, observational study to compare the efficacy of methylnaltrexone between patient groups using different types of opioids. The immunomodulatory and anti-angiogenic effects of methylnaltrexone will be evaluated in a subset of patients included in the VU University medical center. The trial will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and has been approved by the Medical research Ethics Committee of the VU University medical center and the institutional ethics committees of the other participating sites. Patient recruitment and data collection started in July 2012. A study flow chart is provided in Figure 1.

Patients

Patients are recruited from the outpatient clinics and the inpatient wards of a University medical center, three teaching hospitals and a high care hospice in the Netherlands. We ask patients for informed consent to participate in this study if they suffer from OIC caused by morphine, oxycodone or fentanyl, despite prophylactic laxative use. Patients should use only one subtype of maintenance opioids, but (short-acting) rescue doses of another opioid subtype are allowed for up to two doses a day. Rescue doses of a short-acting form of the same opioid subtype as the maintenance opioid can be used in any dosing frequency. With this maximum of two doses the rescue opioid will not have a therapeutic level during a significant part of the day.[13]

Patients should be on a stable laxative regimen for at least 3 days before the first dose of methylnaltrexone. This is defined as at least one type of laxative in an adequate dosing regimen, (e.g. macrogol 2 packets daily, magnesium(hydr)oxide 500 mg three times daily, bisacodyl 10 mg daily or sennoside A + B 10 ml daily) or at least two types of laxatives in a suboptimal dose with patient characteristics hampering optimal treatment.

Further inclusion criteria are that the patient should be aged ≥18 years; receives supportive care for any medical condition that requires prolonged opioid use (e.g. cancer or chronic obstructive pulmonary disease); is able to provide informed consent; has an opioid induced change in his/her laxation pattern with <3 bowel movements in the past week, and no bowel movement in the past 24 hours, or no bowel movement in the past 48 hours.

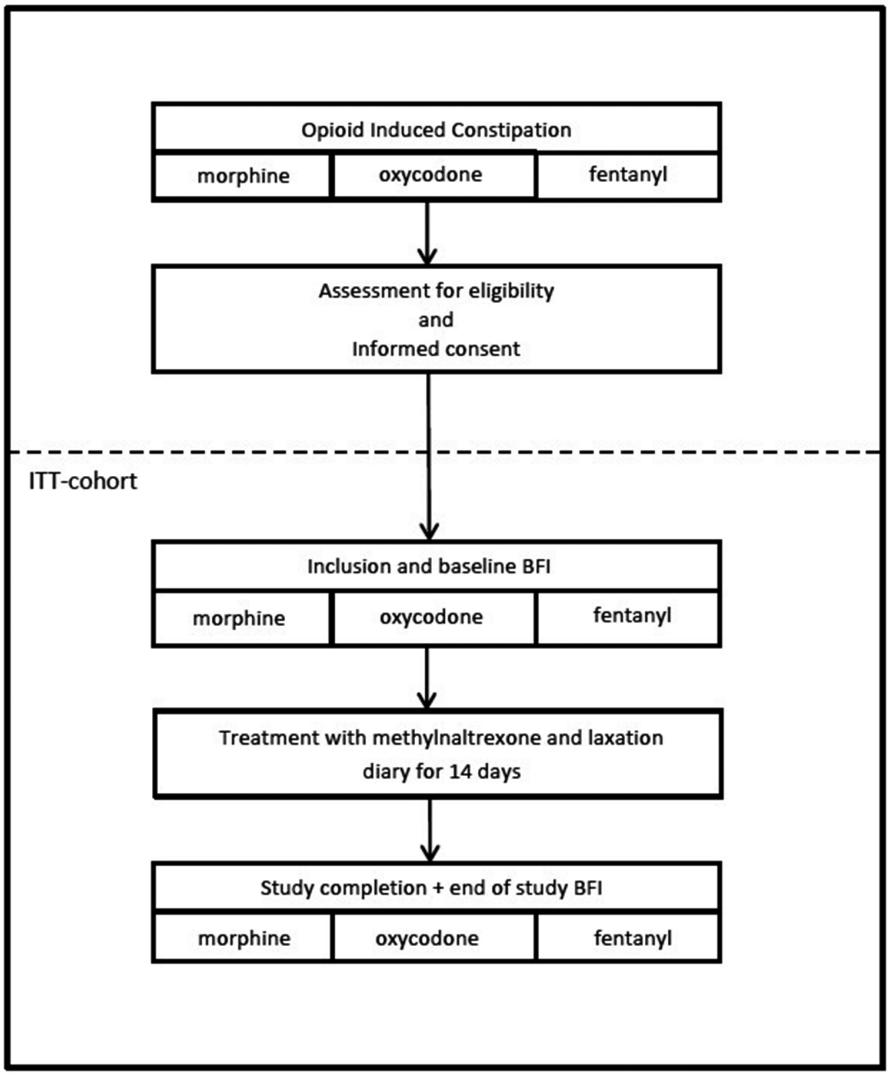

Figure 1. Study flow chart

Exclusion criteria for participation are previous treatment with methylnaltrexone; a life expectancy of less than two weeks; presence of a fecal ostomy or an intraperitoneal catheter; clinically relevant active diverticular disease; body weight <38 kg; and contra-indications for methylnaltrexone use, such as a suspected mechanical gastrointestinal obstruction, impaired renal function (eGFR <30 ml/min/1.73 m^2 or requiring dialysis), pregnancy or lactation, treatment with an investigational product, and presence of another, more probable cause of constipation. Presence of the latter is discussed between the patients physician and the investigator, and if necessary additional imaging or laboratory analysis is performed. Patients should be excluded if there are clinical abnormalities present that may interfere with participation or compliance to the study.

Additional exclusion criterion for the laboratory part of the study is the use of immunomodulatory drugs, such as chemotherapy and tyrosine kinase inhibitors in the past four weeks, or the use of corticosteroids ≥ 30 mg prednisolone or equivalent in the past two weeks.

Randomization, blinding and treatment allocation

Since all patients have an indication for treatment with methylnaltrexone and literature has already shown better responses to methylnaltrexone than to placebo, there will be no placebo treatment arm.

All patients receive the same dosing schedule of methylnaltrexone; there will be no randomization or blinding procedure. Study groups are defined by the type of opioid used by the patient, being either morphine sulphate, fentanyl or oxycodone.

Treatment

Patients will be treated with methylnaltrexone in a standard dosing regimen for their weight:

- 38–62 kg: 8 mg
- 62–114 kg: 12 mg
- >114 kg: 0.15 mg/kg

Methylnaltrexone will be administered subcutaneously every other day for up to 7 doses. Treatment with methylnaltrexone will be continued for up to 14 days. If desired, the patient may continue methylnaltrexone treatment after finishing the 14-day study treatment.

While enrolled in this study, it is not allowed to use rescue laxatives or enemas 4 hours before and/or after methylnaltrexone administration. Rescue laxatives are defined as laxatives which are not prescribed on a regular basis at the start of the study, and might be needed if methylnaltrexone is not effective. Standing laxative orders and opioid treatment will be continued during the study, but can be modified according to clinical judgment if diarrhea occurs or constipation persists. If needed, opioid dosing can be increased, however not decreased to a level below baseline. The use of spasmolytic drugs to relieve abdominal cramps is permitted in this trial.

Study measurements

Demographic and baseline data of each patient will be extracted from his/her medical record and checked with the patient. These will include the medical condition for which the patient uses opioids, the daily dose of the specific opioid subtype the patient uses, and the type and dose of laxatives the patient uses.

Patients will be asked to complete a laxation diary from day −3 up to day 14, and the Bowel Function Index (BFI) on day 0 and 14. In the laxation diary the time of administration of methylnaltrexone is noted, as well as the timing, consistency and volume of bowel movements. Patients also note an average pain score for each day, the occurrence of side effects and use of rescue laxatives in the laxation diary. The BFI consists of three questions about symptoms of constipation experienced during the past week. Answers to these questions are rated on a scale from 0 to 100 and the final

score is calculated by the mean of the three answers. A decrease of 12 points or more between start and end of the study is thought to be a clinically significant response.[32]

From patients taking part in the exploratory study, blood will be drawn before the first administration of methylnaltrexone (day 0), after 24 hours (day 1), at day 14 and around day 42 for immuno- and angiogenic measurements.

Non-responders

If the patient has no response to the first 4 administrations of methylnaltrexone (first week of treatment) the treatment will be halted. Patients should still complete the diary and BFI according to the study schedule.

Adverse events

Adverse events are defined as any undesirable experience occurring to a patient during the study, whether or not considered related to the treatment. All adverse events reported spontaneously by the patient or observed by the investigator or his staff will be recorded and graded according to the common terminology criteria for adverse events version 4.0. All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

Diarrhea, abdominal cramps or sudden increase of pain grade 3 according to the Common Terminology Criteria for Adverse Events (CTCAE), that is related to the study drug according to the investigator, could be reason to skip the next dose of methylnaltrexone.

If these side-effects re-appear after the following dose, the treatment with methylnaltrexone should be halted. Patients will be asked to complete the laxation diary and BFI according to the study schedule. Patients participating in the laboratory part of the study will be withdrawn from this part of the study.

Diarrhea, abdominal cramps or sudden increase of pain grade 4 according to the CTCAE, that is related to the study drug according to the investigator, would be reason to stop treatment with methylnaltrexone. Patients will be asked to complete the laxation diary and BFI according to the study schedule, if possible. Patients participating in the laboratory part of the study will be withdrawn from this part of the study.

Endpoints

Primary endpoint is the proportion of patients that has a rescue-free laxation response within 4 hours after at least 2 of the first 4 doses (the first week of treatment). Secondary endpoints are the time to first laxation, response percentages within 4 or 24 hours after the first and consecutive methylnaltrexone administrations, the number of laxations per week and the change in BFI score between day 0 and 14.

Additional study parameters are the change in leukocyte subsets and serum cytokine levels, angiogenic blood factor concentrations, level of endothelial progenitor cells, and angiogenic potential determined with in vitro endothelial cell proliferation assays.

Sample size calculation and statistical analysis

Opioid treatment may cause constipation, but constipation may also have another etiology. In calculating the number of patients per group we assumed OIC in constipated patients treated with fentanyl to be 40% and in patients treated with morphine sulphate or oxycodone to be 70 and 75%.[8] Based on the receptor-profile and pharmacokinetics of the different opioids[13] we hypothesize that methylnaltrexone will induce successful laxation in 60% of the patients in the morphine group, 60% of the patients in the oxycodone group and in 25% of the patients in the fentanyl group within 4 hours after at least 2 of the first 4 doses (Table 2). For testing two hypotheses, being a 35% difference in response rate between the morphine group vs. the fentanyl group and a 35% difference in response rate between the oxycodone group vs. the fentanyl group, we used a corrected α of .025 instead of .05. This hypotheses will be tested against the null-hypothesis that there is no difference between the efficacy of methylnaltrexone between the different opioid subtypes. Calculation of the sample size performed with STATA 11, using a power of 0.8 and an α of .025 in a two sided test, results in 62 patients in the morphine sulphate group, 62 patients in the oxycodone group and 31 patients in the fentanyl group. Taking into account an expected drop-out rate of 20% we aim to include 78, 78 and 39 patients respectively.

Based on the sample size of the three groups it seems feasible to include 20 patients of each group in the exploratory part of the study, in which the immunologic and angiogenic effects of methylnaltrexone are studied. This sample size seems to be large enough to account for the inter individual differences in the results found in previous studies on this subject.

Data will be anonymized and collected in a web-based database system (Open Clinica). Statistical analysis will be performed in SPSS version 20. The primary endpoint will be expressed in the proportion of patients having rescue-free laxation response within 4 hours after at least 2 of the first 4 doses and significance will be evaluated by the χ^2 test.

The proportion of patients fulfilling the secondary end points will also be evaluated by the χ^2 test. The time to laxation, the number of laxations per week, the change in BFI score and the data from the laboratory part will be continuous variables and will therefore be presented by their mean

Table 2. Expected response rate to methylnaltrexone

Opioid	Probability that constipation is opioid induced	Occupation of the peripheral μ receptor by opioid subtype	Expected response rate to methylnaltrexone
Morphine Sulphate	70%	High	60%
Oxycodone	75%	Intermediate-high	60%
Fentanyl	40%	low	25%

Based on the data in Table 1, we expect a high probability that the constipation is opioid induced for morphine sulphate and oxycodone. This is in contrast with a low probability that it is opioid induced for fentanyl. Because morphine sulphate primarily acts on the peripheral mu receptor, we expect a good response rate to methylnaltrexone. The combination of a high probability that the constipation is opioid induced in the oxycodone group, with its activity on both the central and the peripheral mu, kappa, and gamma receptor leads to an expected response rate that equals that of morphine sulphate. For the fentanyl group both the low probability that the constipation is opioid induced, and the sequestration in the central nerve system lead to a very low expected response rate to methylnaltrexone.

and standard deviation and analyzed by means of the student *t*-test, Mann–Whitney *U* test, or ANOVA, whichever is considered most appropriate.

DISCUSSION

Constipation is one of the most common symptoms in palliative care, and is frequently caused by opioids. Despite prophylactic laxatives, up to 20 percent of patients using opioids will develop opioid induced constipation (OIC). Methylnaltrexone, a peripherally acting μ-opioid receptor antagonist, is designed to displace the opioid from peripheral receptors in the gut, thereby decreasing the opioid's constipating effects and inducing laxation, without reducing analgesia.

In current practice it is used as rescue medication after failure of standard (combination) laxative therapy. Methylnaltrexone prescribed in an earlier stage could avoid severe OIC symptoms. The reasons for this rescue strategy are mainly based on the fact that methylnaltrexone has only been tested as rescue medication for OIC and that the costs of methylnaltrexone are higher than those of other laxatives. Reports of gastrointestinal perforations after use of methylnaltrexone might have resulted in more reluctance to prescribe this drug.[33] Another important factor that tempers the use of methylnaltrexone is the observation that only half of the patients respond to this treatment. We hypothesize that the response rate is dependent on the receptor profile of the opioid that is causing constipation. Consequently, it should be possible to optimize clinical benefit of methylnaltrexone by prescribing this in an earlier stage of constipation treatment to patients who are likely to respond. In this study we will evaluate differences in efficacy of methylnaltrexone in reducing OIC between the commonly prescribed opioid subtypes morphine sulphate, oxycodone and fentanyl.

As this is a prospective study, we have the benefit of adequate power compared to a subset analysis of previous studies. We will evaluate the objective response (number of laxations) in combination with the clinical benefit as is rated on the Bowel Function Index.

In this study the opioid subtypes the patients are using are not randomized, but based on the preference of the treating physician and the side effects experienced by patients. Although this might influence the incidence of OIC, it should not influence the efficacy of methylnaltrexone for a specific opioid subtype.

We have not included a placebo treatment group, because methylnaltrexone is already proven effective and cannot be withheld from patients for ethical reasons.

In this study rescue opioids of a different subtype than the maintenance opioid are allowed, with a maximum of two rescue doses per day. This decision is based on the fact that in daily practice a majority of patients use opioid combination regimens with a difference in prescribed subtypes of rescue- and maintenance opioids. We have set a cut-off at two rescue-opioid doses a day. This is based on the pharmacokinetic properties of rescue opioids, which will not have therapeutic levels during a significant part of the day when they are administered twice a day.[13] The possibility that these rescue opioids contribute to the development of OIC, even in these low doses, can however not be ruled out.

The exploratory laboratory part of this study is of particular interest when the anti-angiogenic and immunomodulatory effects found in pre-clinical studies are clinically confirmed. If methylnaltrexone inhibits this pro-angiogenic and immunomodulatory effects of opioids, a randomized controlled trial investigating the effects of opioids with or without methylnaltrexone on tumor progression and survival could be a next step.

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6

OPTIMAL TREATMENT OF OPIOID INDUCED CONSTIPATION IN DAILY CLINICAL PRACTICE – AN OBSERVATIONAL STUDY

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ABSTRACT

Background

Opioids are prescribed in over 40% of patients with advanced cancer, but side effects occur frequently. In this study we evaluated the development and treatment of opioid induced constipation (OIC), and OIC resolving effect of methylnaltrexone for different opioid subtypes in daily clinical practice.

Methods

Patients with cancer using opioids were included in a retrospective chart analysis. Baseline characteristics, data on opioid use, laxative use, and OIC were collected. Patients with OIC who were prescribed methylnaltrexone, were included in a prospective observational trial (NCT01955213).

Results

Thirty-nine of 327 patients (pts) with cancer who were treated with opioids suffered from OIC (overall prevalence 12%; 95%-CI: 8–15%). The prevalence of OIC was similar in patients treated with oxycodone or fentanyl (12 of 81 pts. vs. 18 of 110 pts., RR 0.9; 95%CI 0.4–2.0). The morphine equivalent daily dose did not significantly differ between opioid subtypes (fentanyl 89 mg (IQR 60–180) vs. oxycodone 40 mg (40–80), P = 0.231). Twenty-two individual patients (7%) were admitted for OIC. Most effective laxatives in admitted patients were enemas, methylnaltrexone, or 4-l polyethylene-glycol solution. In the prospective observational study, the effect of methylnaltrexone could be evaluated in 23 patients. Eleven patients achieved the primary endpoint of ≥2 laxation responses out of the first four doses methylnaltrexone, independent of opioid subtype.

Conclusions

OIC is a burdensome clinical problem independent of opioid subtype. Timely intensification of prophylactic laxative treatment, especially when opioid doses increase, may help to prevent OIC. Clinically overt OIC requires a more intensive laxative regimen with for example methylnaltrexone.

Trial registration

NCT01955213.

BACKGROUND

Over 40% of patients with advanced cancer need opioids at some point during their disease trajectory.[1,2] Opioids may cause transient side effects such as nausea and drowsiness.[3] A non-transient side effect of opioids is constipation.[3] Opioid induced constipation (OIC) is caused by binding of opioids on the μ-receptor in the intestines, leading to a decrease in peristaltic movements and a longer transit time, allowing more water absorption from the stool.[4] Differences in biodistribution and opioid receptor binding profile result in varying incidence rates of OIC between different opioid subtypes.[5] While patients included in trials are frequently prescribed single opioids, in daily practice, combinations of different opioid subtypes are used to tailor pain management and to optimize ease of use. Different laxatives are also prescribed in variable doses in line with international guidelines advising to prescribe prophylactic laxatives when opioids are being used.[6,7] Most used laxatives are osmotic agents e.g. polyethylene glycol (PEG) or magnesium oxide, and stimulant laxatives e.g. bisacodyl. Adherence to the guidelines by physicians varies,[8] and patients frequently stop using these prophylactic laxatives due to diarrhea.[9,10] Even more, other patient- or treatment-related factors may cause constipation in patients with cancer using opioids, such as reduced fluid intake, or the use of 5-HT3 receptor antagonists for chemotherapy induced nausea and vomiting. Real life data on the prevalence of constipation, and more specific opioid induced constipation, in patients with cancer using opioids are scarce,[10-12] and comparative trials evaluating different treatment options for OIC have not yet been conducted.

The optimal treatment strategy for constipation depends on its cause in an individual patient.[6] Various strategies to treat OIC are available, including to start, add, or increase the dose of laxatives; to admit patients to the hospital for more intensive laxation treatment; to decrease the dose of opioids (which is often not feasible); to switch to another opioid subtype; or to use various formulations of the μ-opioid receptor antagonist naloxone.[7,13] Naloxone has been used in the past for opioid induced constipation, but its use was associated with opioid withdrawal and decreased pain relief.[14] As an alternative methylnaltrexone, a quaternary amine of naltrexone that does not cross the blood-brain barrier, can be prescribed. It can be used as a peripheral μ-receptor antagonist which resolves OIC in 50% of patients, without influencing the analgesic effect achieved by the central effects of the opioid.[14,15]

In this study we evaluated the development and treatment of opioid induced constipation in daily clinical practice, and the OIC resolving effect of methylnaltrexone for different opioid subtypes. We performed a retrospective chart review evaluating real-life data on opioid use and the incidence of OIC in every day clinical practice, and the effect of different treatment options for OIC. In addition, a prospective observational trial was set up to study the effect of methylnaltrexone for OIC caused by different opioid subtypes, in order to determine which patients could benefit most from this treatment.[5]

METHODS

Retrospective chart review

Patients who were prescribed opioids by their oncologist at an academic hospital and a large teaching hospital over a six month period in 2014 were included in the retrospective study. Data

concerning baseline characteristics, opioid and laxative use, and the occurrence of OIC were extracted from the patient charts. When multiple opioid prescriptions were made in the study period, the prescription with the highest oral morphine equivalent daily dose (MEDD) was used for this analysis. Conversion rates from buprenorphine, fentanyl, subcutaneous morphine, oxycodone and tramadol to oral morphine were 2.29, 2.4, 3, 3, and 0.2, respectively.[16] For methadone conversion rates to oral morphine were 4 for doses <22.5 mg, 6 for doses between 22.5 and 50 mg, and 8 for doses >50 mg .[16] Notes on the patient's laxation pattern in the period between 30 days before and after the selected opioid prescription were extracted to evaluate if OIC had occurred. Admittances for OIC were registered for the year prior to and following the selected opioid prescription. In order not to miss admittances with OIC as an underlying cause, we reviewed each admission for the mentioning of (opioid-induced) constipation as a underlying cause for the reason of admission. Constipation was defined as a reported change in laxation frequency to less than 3 stools per week. Due to the retrospective nature of this part of the study, subjective components to constipation could not be assessed. Constipation was considered as opioid induced if this was made explicit in the patient chart, and/or if there was no other major contributing factor specified (e.g. dehydration, obstruction of the GI-tract by a tumor or carcinomatous peritonitis, or side effects from other drugs).

Sample size and statistics

Most of the presented data are descriptive. It was expected that, even despite prophylactic laxative use, patients using fentanyl would have a lower incidence rate of OIC than patients using oxycodone;[5] 10% of the patients using fentanyl would develop OIC, compared to 30% of the patients using oxycodone. In a population in which 40% used fentanyl and 25% oxycodone, a study sample with at least 120 patients using fentanyl and 80 using oxycodone was needed to have 90% power to detect the hypothesized difference in the incidence of OIC between fentanyl and oxycodone ($P < 0.05$ was considered statistically significant). Descriptive data are presented by their mean or median, and SD or inter quartile range (IQR). Comparisons were made with a Pearson's χ^2 test or Mann-Whitney U test, as considered appropriate. For assessing the effect of multiple factors, multiple logistic regression was used.

Prospective observational study

The methods of the observational trial to determine the differences in the effect of methylnaltrexone on OIC induced by different opioid subtypes are published elsewhere.[5] Briefly summarized, patients with OIC caused by morphine, oxycodone, or fentanyl, without contra-indications for methylnaltrexone, received a 14-day treatment with methylnaltrexone subcutaneously (SQ) every other day. In this period a laxation diary was kept to monitor the effect of methylnaltrexone. The Bowel Function Index questionnaire (BFI)[17] was completed at the start and end of this treatment period. We aimed to include 78 patients in the oxycodone group, 78 patients in the morphine group and 39 patients in the fentanyl group. This study was approved by the Medical research Ethics Committee of the VU University medical center and performed in accordance with the Helsinki Declaration of the World Medical Association.

BFI questionnaire

The BFI consists of three questions about symptoms of constipation experienced during the past week. Answers to these questions are rated on a scale from 0 to 100 and the final score is calculated by the mean of the three answers. A decrease of 12 points or more between start and end of the study is thought to be a clinically significant response.[5,17]

Software for data storage and analysis

Data of both studies were anonymized and stored in the web based database system Open Clinica (Open Clinica version 3.3). Statistical analyses were performed with IBM SPSS version 22.0 (IBM, Armonk, NY, USA).

RESULTS

Patient characteristics

Three hundred twenty seven patients were included in the retrospective analysis. Characteristics of these patients are presented in Table 1. Fentanyl (N = 131, 40%) and oxycodone (N = 90, 28%) were the most frequently prescribed opioid subtypes. Ninety-four patients (29%) did not use a maintenance opioid, only rescue doses. Tumor types, treatment intention (curative or palliative), intake failure (especially reduced fluid intake), and abdominal innervation problems (paralysis of the intestines) between the fentanyl and oxycodone group were significantly different. For fentanyl maintenance treatment continuous-release patches were used. These were mostly prescribed for patients treated with chemo-radiotherapy for head and neck cancer, which explains most differences in characteristics between the treatment groups. When correcting for this tumor type, only intake failure remained statistically significant more frequent in the patients using fentanyl patches (28/95 vs. 8/85 in the oxycodone group, P = 0.001), and abdominal innervation problems were more frequent in the oxycodone group (7/85 vs. 1/95 in the fentanyl group, P = 0.017).

Sixty percent of the patients used concurrent laxatives, mostly a polyethylene-glycol solution (PEG), magnesium oxide, and/or enema's (55, 7, and 6% respectively, Table 2). Thirty-one patients (9%) used two or more types of laxatives. There were no statistically significant differences in the number of patients using a specific laxative, nor in the dose of laxatives, between patients using fentanyl or oxycodone, except for the dose of magnesium which was higher in patients using oxycodone (N = 5) than in patients using fentanyl (N = 13) (median 6 vs. 3 tablets per day, P = 0.033).

When converted to oral morphine equivalent daily dose (MEDD), the median dose of regularly taken opioids was 60 mg (IQR 29–120). Two-hundred-and-ninety-one patients (89%) were prescribed rescue opioids, mostly short-acting oxycodone (n = 185, 57%).

Opioid induced constipation

For 257 patients (79%) the attending physician made a note in the patient's chart on their laxation pattern. Sixty-eight patients (21%) were constipated, of whom 39 (12%) were considered to be constipated due to opioids (Table 3). OIC was equally prevalent in patients treated with oxycodone or fentanyl (12 of 81 pts. vs. 18 of 110 pts., RR 0.9, 95% CI 0.4–2.0). Although there was a statistically

Table 1. Patient characteristics - retrospective chart review

		Total *N* = 327 (%)	Fentanyl Maintenance *N* = 131 (%)	Oxycodon maintenance *N* = 90 (%)	*P* (fentanyl vs. oxycodone)
Age	mean (SD)	63 (12)	64 (11)	63 (12)	0,368
Sex	Male	146 (45)	64 (49)	41 (46)	
	Female	181 (55)	67 (51)	49 (54)	0,629
Cancer type	Gastro-intestinal	110 (34)	43 (33)	26 (29)	
	Breast	54 (17)	13 (10)	19 (21)	
	Genito-urethral	62 (19)	23 (20)	26 (29)	
	Skin	15 (5)	7 (5)	5 (6)	
	Lung	1 (0)	1 (1)	0 (0)	
	Head&Neck	53 (16)	33 (25)	5 (6)	
	Brain	3 (1)	1 (1)	0 (0)	
	Sarcoma	6 (2)	2 (2)	2 (2)	
	Other	23 (7)	5 (4)	7 (8)	0,005*
Treatment intention	Curative	71 (22)	37 (28)	9 (10)	
	Palliative	256 (78)	94 (72)	81 (90)	0,001*
Current Treatment	Follow-up	7 (2)	3 (2)	1 (1)	
	Watchfull waiting	22 (7)	7 (5)	5 (6)	
	Chemotherapy	90 (28)	32 (24)	28 (31)	
	Radiotherapy	15 (5)	7 (5)	5 (6)	
	Chemoradiotherapy	38 (12)	25 (19)	3 (3)	
	Targetted therapy	51 (16)	17 (13)	17 (19)	
	Best supportive care	81 (25)	33 (25)	24 (27)	
	Other	23 (7)	7 (5)	7 (8)	0,032*
ECOG performance status	0	14 (4)	3 (2)	7 (8)	
	1	110 (34)	40 (31)	36 (40)	
	2	67 (21)	22 (17)	20 (22)	
	3	29 (9)	14 (11)	11 (12)	
	4	17 (5)	6 (5)	1 (1)	
	Unknown	90 (28)	46 (35)	15 (17)	0,264
Contributing factors	Peritoneal tumor depositions	52 (16)	21 (16)	13 (14)	0,748
	Intestinal metastasis	19 (6)	8 (6)	3 (3)	0,352
	Involvement of other abdominal organs	115 (35)	45 (34)	34 (38)	0,602
	Hypercalcemia	21 (6)	13 (10)	6 (7)	0,239
	Reduced mobility	116 (36)	47 (36)	34 (38)	0,773
	Intake failure	71 (22)	41 (31)	9 (10)	<0,001*
	Constipating co-medication	75 (23)	30 (23)	18 (20)	0,607
	Abdominal innervation problems	11 (3)	1 (1)	7 (8)	0,006*
	Bowel disease	4 (1)	1 (1)	1 (1)	0,789
	Depression	3 (1)	2 (2)	0 (0)	0,239

Table 1. (continued)

		Total *N* = 327 (%)	Fentanyl Maintenance *N* = 131 (%)	Oxycodon maintenance *N* = 90 (%)	*P* (fentanyl vs. oxycodone)
Pain Score[1]	NRS 0-10, mean (SD)	4,0 (6,0)	4,0 (5,0)	5,0 (6,5)	0,948
Opioid doses[2]	Maintenance dose[3], median (IQR)	60 (29-120)	60 (29-120)	40 (40-80)	0,006*
	Rescue dose[3]	20 (3-40)	23 (10-50)	20 (0-40)	0,259
Rescue opioid subtypes	No rescue opioid	36 (11)	9 (7)	6 (7)	
	Buprenorfine	14 (4)	0 (0)	0 (0)	
	Fentanyl	24 (7)	17 (13)	3 (3)	
	Methadon	2 (1)	0 (0)	0 (0)	
	Morphine	57 (17)	34 (26)	5 (6)	
	Oxycodon	185 (57)	71 (54)	76 (84)	
	Tramadol	5 (2)	0 (0)	0 (0)	
	Other	4 (1)	0 (0)	0 (0)	<0,001*

[1] Pain score at a numerical rating scale (NRS) from 0-10 at the moment the opioid was prescribed (*N*=115)

[2] Oral morphine equivalent daily doses (MEDD) at the moment of opioid prescription

[3] Rescue opioid doses, calculated for patients with a known rescue frequency (total *N*=135, fentanyl *N*=64, oxycodone *N*=30)

significant difference in the oral morphine equivalent daily dose (MEDD) of regularly taken opioids between patients using fentanyl and oxycodone at opioid prescription (fentanyl MEDD 60 mg (IQR 29–120), oxycodone MEDD 40 mg (IQR 40–80), P = 0.006), the difference in the MEDD at diagnosis of OIC was not statistically significant (fentanyl 89 mg (IQR 60–180) vs. oxycodone 40 mg (IQR 40–80), P = 0.231). When analyzing the effects of opioid subtypes fentanyl and oxycodone and MEDD on OIC in a multiple logistic analysis, none showed statistical significance (OR for the risk at OIC for MEDD 0.997 (95% CI 0.990–1.005); for fentanyl 1.310 (95% CI 0.351–4.892); and for oxycodone 4.086 (95% CI 0.630–26.495)). Also, no difference in OIC was found between patients using oxycodone or fentanyl as rescue opioid (13% vs. 9%, P = 0.554).

In the majority of the patients with OIC, the opioid dose remained stable (N = 14) or was increased (N = 14). In 32 patients diagnosed with OIC (82%) the laxative treatment was adjusted, mostly by prescribing a new laxative (N = 20). The main reason not to alter the laxative treatment while a patient was diagnosed with OIC, or to even stop the laxative treatment, was that the patient had entered the terminal phase and was not able to take oral medication anymore (N = 6).

Admission for OIC

Twenty-two individual patients (7%) were admitted to the hospital for OIC (Table 3). The median MEDD at admission was 70 mg (IQR 40–180). Eleven patients used fentanyl, with a median MEDD of 180 mg (IQR 60–180). Five patients used oxycodone, with a median MEDD of 60 mg (IQR 40–140). The difference between the doses of fentanyl and oxycodone at admission was not statistically significant (P = 0.145). The opioid prescription was adjusted because of OIC in 4 of the 22 patients; in one patient the dose was lowered, in three patients an opioid rotation was performed.

Table 2. Laxative use at opioid prescription

	Total *N* = 327 (%)	Fentanyl maintenance *N* = 131 (%)	Oxycodone maintenance *N* = 90 (%)	*P* (fentanyl vs. oxycodone group)
Any laxative	195 (60)	88 (67)	63 (70)	0,657
Macrogol	181 (55)	78 (60)	60 (67)	0,283
Macrogol dose, median[1]	1	1	1	
Magnesium	23 (7)	13 (10)	5 (6)	0,243
Magnesium dose, median[2]	3	3	6	
Bisacodyl	3 (1)	3 (2)	0 (0)	0,148
Bisacodyl dose, median[3]	1	1	.	
Lactulose	7 (2)	3 (2)	2 (2)	0,973
Lactulose dose, median[4]	1	1	2	
Enema's	18 (6)	5 (4)	7 (8)	0,202
Enema frequency, median[5]	1	1	1	
Other	3 (1)	2	0 (0)	0,239

[1] Number of macrogol sachets per day. Sachet à 13,7 g containing macrogol 3350 13,125 g and elektrolytes (potassiumchloride, sodiumchloride, sodium hydrogen carbonate). Inter quartile range (IQR) total group: 1-2; fentanyl group: 1-2; oxycodone group: 1-2.

[2] Number of magnesium oxide tablets à 500 mg per day. IQR total group: 2-6; fentanyl group 2-3; oxycodone group: 4-6.

[3] Number of bisacodyl tablets à 5 mg per day. Range total group: 1-1; fentanyl group: 1-1; oxycodone group: not applicable.

[4] Number of lactulose doses per day. One dose equals 15 ml of lactulose 670 mg/ml. Range total group: 0-2; fentanyl group: 0-2; oxycodone group: 0-2.

[5] Number of enema's per day, usually a sodium phosphate enema of 133 ml containing 31,8 mg sodium acid phosphate and 139,1 mg sodium dihydrogenphosphate per ml. IQR total group: 0,5-1; fentanyl group: 0-1; oxycodonde group: 0,5-1.

Patients admitted for OIC were mostly treated with enema's (N = 16) and a 4-l polyethylene glycol solution (N = 11). Complete resolution of constipation was seen with enema's (N = 5/16), methylnaltrexone SQ (N = 2/5) and with a 4-l polyethylene glycol solution (N = 2/2).

Effect of SQ methylnaltrexone in different opioid subtypes

Twenty-six patients were included in the methylnaltrexone trial between July 2012 and December 2015. Baseline characteristics of the included patients are presented in Table 4. Sixteen patients used oxycodone, eight fentanyl and two morphine. Three patients were lost to follow-up because the laxation diary was not returned (two in the fentanyl group, one in the oxycodone group). Of the 23 patients who returned response data of at least one dose of SQ methylnaltrexone, 11 met the primary endpoint of at least 2 laxation responses out of the first 4 doses. These were 8 patients in the oxycodone group (8 of 15 pts., 53%), 2 in the fentanyl group (2 of 6 pts., 33%) and 1 in the morphine group (1 of 2 pts., 50%). Reasons to prematurely stop SQ methylnaltrexone treatment were: per patient request (N = 4), adverse events (N = 2: 1 diarrhea, 1 abdominal pain), intercurrent illness (N = 1), death due to disease progression (N = 1), and unknown (N = 1).

Table 3. Opioid Induced Constipation

Opioid maintenance type[1]	*N*=	Note on laxation pattern *N* (%)[2,3]	Morphine dose (MEDD)[4] median (IQR)	Constipation[5] *N* (%)	MEDD[4,6] median (IQR)	Opioid Induced Constipation[7,8] *N* (%)	MEDD[9] median (IQR)	Admission for OIC[10] *N* (%)[11]	MEDD[12] median (IQR)
No maintenance opioid	94	77 (82)	0 (0)	12 (13)	0 (0)	1 (1)	0 (0)	1 (1)	0
Buprenorfine	16	16 (100)	105 (31-180)	5 (31)	24 (17-98)	3 (19)	30 (17-120)[13]	2 (13)	54 (17-90)[15]
Fentanyl	110	86 (78)	89 (60-150)	25 (23)	89 (60-180)	18 (16)	89 (60-180)	11 (10)	180 (60-180)
Methadon	3	2 (67)	60 (60-240)[13]	2 (67)	120 (60-240)[13]	1 (33)	240 (0)	0 (0)	n.a.
Morphine	5	3 (60)	60 (40-96)	3 (60)	60 (40-96)[13]	2 (40)	68 (40-96)[13]	3 (60)	60 (40-80)[15]
Oxycodon	81	64 (79)	40 (40-80)	19 (23)	40 (40-80)	12 (15)	40 (40-80)	5 (6)	60 (40-140)
Tramadol	14	7 (50)	30 (20-40)	1 (7)	20 (0)	1 (7)	20 (0)	0 (0)	n.a.
Other	4	2 (50)	7 (5-10)[13]	1 (25)	n.a.[14]	1 (25)	n.a.[14]	0 (0)	n.a.
Total	327	257 (79)	60 (40-120)	68 (21)	60 (40-120)	39 (12)	60 (40-120)	22 (7)	70 (40-180)

[1] Opioid maintenance type at note on laxation pattern or at prescription (if no note was found in the patient records)

[2] Number of patients in each subtype for whom a note was made at their laxation pattern, *P*=0.931

[3] Percentage of patients with a note on their laxation pattern for each opioid subtype

[4] Oral Morphine Equivalent Daily Dose (MEDD) in milligrams

[5] Number of patients with a diagnosis of constipation in each opioid subtype, *P*=0.030

[6] The difference between the fentanyl group and the oxycodone subgroup was statistically significant, *P*=0.043

[7] Number of patients with a diagnosis of opioid induced constipation (OIC), *P*=0.006

[8] Percentage of patients with a diagnosis of opioid induced constipation for each opioid subtype

[9] The difference in MEDD of patients using fentanyl or oxycodone was not statistically significant, *P*=0.231

[10] Opioid subtype the papient was using at admission for OIC

[11] Percentage of patients admitted for OIC relative to the number of patients using this opioid subtype at the moment of the opioid prescription included in this analysis

[12] Oral Morphine Equivalent Daily Dose (MEDD) at the moment of admission for OIC; IQR= inter quartile range

[13] Range instead of interquartile range, due to low number of patients using this opioid subtype

[14] The MEDD could not be calculated because the conversion rate for this opioid subtype is unknown

[15] Range instead of inter quartile range, due to the low number of patients using this opioid subtype

Table 4. Patient characteristics methylnaltrexone trial

		Total *N*=26	Oxycodone group *N*=16	Fentanyl group *N*=8	Morphine group *N*=2
Age	mean (SD)	59 (13)	58 (10)	58 (18)	62 (18)
Sex	Male	11	9	2	0
	Female	15	7	6	2
Treatment setting	Hospital	20	11	7	2
	Ambulant	6	5	1	0
Cancer Type	Gastro-intestinal	9	6	3	0
	Breast	6	3	2	1
	Genito-urethral	6	5	1	0
	Other	5	2	2	1
Concomitant laxatives	Macrogol	19	12	5	2
	Magnesiumoxide	7	4	3	0
	Other	3	3	0	0
Patients using >1 laxative		4	3	1	0
Morphine equivalent daily dose	median (range)	80 (40-540)	80 (40-160)	120 (60-240)	525 (510-540)

Bowel function index (BFI)

Fourteen patients completed the BFI questionnaire on day 0 and 14 (2 in the fentanyl group, 1 in the morphine group, and 11 in the oxycodone group). The median change between start and end of study was −5.8 points (IQR −42.1 to 13.8), where a 12-point decline was previously defined as a clinically significant improvement. There were no statistically significant differences in BFI changes between patients who did or did not meet the studies primary endpoint (median ΔBFI 0.8 vs. -6.7 respectively, P = 0.573).

DISCUSSION

To our knowledge, this is the first study in which the frequency of OIC in real life in an unselected population of patients with cancer is being evaluated. In a study by Wirz et al.[10] and a survey by Bell et al.[12] among long term opioid users with a wide range of diseases data on this subject were limited to secondary endpoints in clinical trials. Bell et al. found that 81% of the 322 included patients (a selection from 130,293 originally invited patients) suffered from constipation despite laxative use, but it remained unclear to what extent the constipation was opioid induced. Wirz et al. performed a prospective observational study in ambulatory patients with cancer referred to the pain clinic. This study revealed a 5,7% incidence rate of constipation in a highly selected group of ambulatory patients using stable opioid doses >28 days, without the need for break-through opioids, and who were not undergoing chemo- or radiotherapy treatment.[10]

In our retrospective chart review 21% of the 327 patients with cancer using opioids suffered from constipation, which was opioid induced in 12% (39 patients). Eighty-seven percent of these

patients (34 of 39 pts) developed OIC despite laxative use. The doses of prophylactic laxatives in this study group were relatively low (e.g. a single polyethylene glycol solution once per day). Therefore, intensification of the prophylactic laxative treatment, especially when the opioid dose increases, might help to reduce the number of admissions for OIC. However, when a patient is admitted for OIC, dose increases of these laxatives do not seem to resolve the problem. At this point more intensive treatments, such as a 4-l polyethylene glycol solution, enemas, and possibly SQ methylnaltrexone, are more effective.

Our hypothesis that OIC occurs more often in patients using oxycodone than in patients using fentanyl, was not confirmed. Although the median MEDD of patients using fentanyl was more than twice the median MEDD for the patients using oxycodone at the moment patients were diagnosed with OIC, this difference was not statistically significant. Therefore, we cannot conclude that oxycodone is more constipating than fentanyl. It might be that the large proportion of patients using oxycodone as rescue opioid next to fentanyl as maintenance opioid has influenced the results, but there were no statistically significant differences found between patients using different subtypes of rescue opioids. This mixture of opioid subtypes reflects real daily practice, which is one of the strengths of this study. Our data complement the findings from opioid and laxative registration studies by providing valuable information on treatment practices and patient characteristics among unselected patients. This information is necessary to guide treatment decisions and for reimbursement and payment decisions.

The results of the chart review are limited to the notes that were made in the patient charts and the hospitals electronic prescription systems. Therefore it is possible that some cases of OIC were missed. Also, data on the actual opioid intake were not available. Based on the low number of records for pain scores noted at the moment of opioid prescription (N = 115 of 327 pts), and the low number of records of the frequency of rescue opioid use (N = 135 of 327 pts), there might be a gap between what is discussed by the patient and the physician, and what is noted in the patient's chart. Other measures to prevent OIC, such as life-style advises, that were discussed with the patient, were not assessed in this study because they were often not recorded in the patient's chart, and compliance to these advises could not be assessed. Another limitation is that most physicians only diagnosed constipation based on a reduced stool frequency. More subjective components of constipation, such as a feeling of abdominal distension, or straining to pass the stool, were given less attention.

The prospective observational study evaluating the efficacy of SQ methylnaltrexone in different opioid subtypes did not reach the anticipated sample size. The results of this trial therefore do not have enough power to draw any conclusions with regard to the hypothesis that patients using fentanyl would have a lower response rate to SQ methylnaltrexone than patients using oxycodone or morphine. The low inclusion rate was due to the significantly lower than expected prevalence of OIC, and the fact that many patients used a combination of different opioid subtypes, which was an exclusion criterion for the study. Contra-indications for SQ methylnaltrexone use were rare. Only 10 patients received all seven methylnaltrexone administrations. The others stopped treatment prematurely due to side effects or the lack of efficacy. There were also a number of patients who requested to stop treatment even though it was effective. These patients did not

suffer from grade 3 side effects, but generally reported a feeling of unease during the first hours after methylnaltrexone administration that may be interpreted as mild side effects or mild opioid withdrawal symptoms. These observed side effects are important for designing possible future studies looking into the effect of μ-opioid receptor blockade on tumor progression.[18]

For clinical practice the results of this study indicate that it is important to ask patients who use opioids regularly about their laxation pattern, and to adjust the prophylactic laxative prescription with increasing opioid doses. Thereby the development of OIC could possibly be prevented or managed in an ambulant setting, instead of requiring a hospital admission.

CONCLUSIONS

In this real-life cohort of patients with cancer, OIC was encountered in 12% of the patients using opioids and lead to a hospital admission in 7%. Timely intensification of prophylactic laxative treatment, especially when the opioid dose increases, might help to further reduce the number of patients with cancer suffering from OIC and may help to prevent hospital admission. Treatment of OIC, once it has developed, requires a more intensive laxative regimen with for example SQ methylnaltrexone, independent of opioid subtype.

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7

AIMING FOR A BETTER UNDERSTANDING AND MANAGEMENT OF CANCER RELATED FATIGUE

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ABSTRACT

Cancer related fatigue (CRF) is a serious symptom of patients with cancer and deteriorates their daily quality of life. While fatigue is a common problem in the general population with a prevalence of about 30 percent, up to 99 percent of patients with cancer suffers from fatigue with more intense severity. CRF is directly related to the biology of cancer, but can also be caused by anticancer treatment. We here review the current evidence on the potential pathophysiological mechanisms causing CRF. Clinical methods to determine presence and severity of CRF and potential treatment options to reduce CRF will be discussed. After reading this review the reader will have knowledge of the current understandings of CRF and will be able to give an evidence based advice to patients suffering from CRF.

INTRODUCTION

Cancer related fatigue (CRF) is a frequently reported, deteriorating complaint in patients with cancer that has a major influence on their daily quality of life. CRF is described as a subjective feeling of tiredness, weakness or lack of energy that influences daily activities and quality of life. In healthy people, fatigue is a functional and protective response to physical or psychological stress. In patients with cancer, fatigue has lost its protective function and does not improve after resting.[1,2] The National Comprehensive Cancer Network (NCCN) defined CRF as: 'a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning'.[3] Others have proposed slightly different definitions including the Fatigue Coalition. They stated that fatigue needs to be disproportionate to recent activities, sufficiently severe to have an impact on daily life, and the symptoms should be a direct consequence of cancer or cancer therapy.[4,5]

CRF is sometimes described as part of a cluster of symptoms together with anorexia, depression, and/or pain.[6] This is, however, mostly done by cluster analysis of symptoms mentioned in literature and clinical relevance has not yet been proven.[6] It has been proposed that CRF is a symptom of depression, but treatment with anti-depressants decreases depression while CRF remains unaffected.[7,8]

EPIDEMIOLOGY

Fatigue is a common problem in the general population. During surveys among patients visiting general practitioners 28 percent report to be fatigued.[9-11] CRF has a prevalence of 15 to 99 percent in patients with cancer, depending on methods used for measuring fatigue and patient group characteristics.[4,12-16] Mendoza *et al* reported that healthy controls consistently rate the severity of their fatigue lower than patients with cancer.[17]

MEASURING CANCER RELATED FATIGUE

Some aspects of CRF can be measured through muscle performance tests. However, to get a more comprehensive measurement of CRF self-report questionnaires can be used.[14,18,19] Forty-three questionnaires (with 55 different names) have been found that were used for measuring CRF and are available in English.[5,12,17-56]

Best established questionnaires for patients with cancer are the EORTC-QLQ-C30 fatigue subscale, the Functional Assessment of Cancer Therapy for Fatigue (FACT-F) and the Fatigue Questionnaire (FQ) (supplement 1).[57] These questionnaires have been validated for their internal consistency, test-retest reliability and sensitivity to change in over 5000 patients, see supplement 1 for more details. The EORTC-QLQ-C30 fatigue subscale is a three item questionnaire that can be used for a quick measurement of fatigue. The FACT-F is a thirteen-item questionnaire containing questions about the level of fatigue and the consequences of fatigue in the past week. The Fatigue Questionnaire is an eleven-item questionnaire with two subscales: physical and mental fatigue. The FQ focuses on the way the patient feels at that particular moment and can therefore be used

on a daily basis. All three questionnaires have shown sensitivity to change over time, but minimal clinically relevant differences are not yet known.

Another questionnaire that has maybe even better psychometric qualities is the Brief Fatigue Inventory (BFI), which has nine items.[12,17,20] This questionnaire is, however, validated in about 1700 patients of which most were non-English speaking.[54]

It is important that questionnaires are easy to understand and can be completed in a minimum amount of time because of the burden a questionnaire can place on fatigued patients. Studies performed with patients that suffer from CRF should therefore report completion rates of the questionnaires, since low completion rates may occur in patients with the highest fatigue levels.

In the clinical setting most patients are asked to rate their fatigue on a Rhoten Fatigue Scale, which is a numerical rating scale that goes from 0 to 10, with 4 or higher as a cut-off point to take further action.[3,12,20,46] This scale can, however, only be used as a screening instrument. For the follow-up of patients treated for CRF, the FACT-F can be used for its excellent psychometric qualities. For follow-up on a daily basis, the FQ would be the best questionnaire.

PATHOPHYSIOLOGY

The pathophysiological mechanism causing CRF has not yet been clarified, but several studies provide circumstantial evidence of factors that might be involved. A summary of these factors are described below and shown in figure 1.

PHYSICAL FATIGUE

In several animal studies, activation of vagal afferent nerves caused reflex inhibition of skeletal muscle activity.[58] This reduced skeletal muscle activity might result in a feeling of general weakness

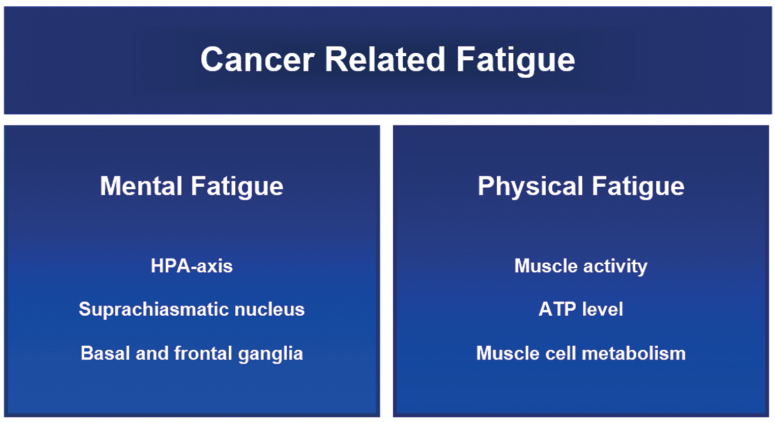

Figure 1. Pathophysiology of CRF. CRF can be divided into mental and physical fatigue. Mental fatigue is mediated by 1) the suprachiasmatic nucleus that controls the 24-hour circadian rhythm under influence of the HPA-axis 2) decreased perfusion of basal and frontal ganglia. Physical fatigue might be result of impaired skeletal muscle activity due to central activation failure and changes in mitochondrial and sarcoplasmic reticulum functioning.

in humans, which can be perceived as fatigue.[58] Cancer and cancer treatment can trigger a peripheral release of neuroactive agents, such as serotonin, several cytokines and prostaglandins, that activate vagal afferent nerves.[59-61]

In addition, tumor activity, cancer treatment and/or cachexia alter skeletal muscle metabolism, which results in dysfunction of the sarcoplasmic reticulum that causes increased intracellular calcium levels and thereby impairment of ATP generation by the mitochondria during muscle contraction.[62] On top of this altered metabolism, anemia and nutritional deficiencies can hamper the supply of nutrients needed for ATP generation. This potential mechanism of CRF was initially supported by a randomized clinical trial in which patients with lung cancer received infusions of ATP and showed improved muscle strength and reduced fatigue.[63] However, these results could not be confirmed in a subsequent trial by Beijer *et al* and therefore should be taken with caution.[64]

Kisiel-Sajewicz et al have recently studied muscle contractile properties of patients suffering from CRF compared to healthy controls. This study shows that the fatigued patients fail earlier in motor tasks, but that this is not associated with changes in contractile properties. This lack of contractile impairment implicates a central activation failure.[18]

MENTAL FATIGUE

Mental fatigue can be triggered by the basal ganglia and the suprachiasmatic nucleus. The basal ganglia influence movement and are involved in motivation. Capuron *et al* show in a study with patients receiving interferon treatment for stage III-IV melanoma, that higher fatigue scores correlate with increased activity levels of the basal ganglia and the cerebellum.[65] Previously, it was shown that patients with depletion of dopamine in these areas also show an increased PET-activity, possibly because of increased oscillatory burst activity.[66] In addition, the blood flow towards the basal ganglia seems to be influenced by cytokines as is shown in patients with MS treated with interferon.[67] The basal ganglia may also play a role in CRF, because many patients with CRF have higher levels of cytokines such as interferon, but to date no trial has been performed in patients with cancer showing evidence for this hypothesis.

Suprachiasmatic nucleus

The suprachiasmatic nucleus is part of the hypothalamus and regulates the 24-hour circadian rhythm via the release of melatonin and daily cortisol curves. Disruption of this 24-hour circadian rhythm has an effect on sleep patterns and quality.[59,68] The suprachiasmatic nucleus is sensitive to the amount of daylight a person receives, but can also be influenced by specific tumor-derived peptides, such as EGF or changes in serotonin and cortisol levels.[59,69,70]

Cortisol and serotonin influence the function of the suprachiasmatic nucleus as part of a complex signaling pathway, which has many feedback loops. Cytokines, especially IL-1β, IL-6 and TNFα, influence almost every step in this pathway. Cortisol activates glucocorticoid cell membrane receptors of the suprachiasmatic nucleus.[71] The activity level of glucocorticoid receptors can be influenced by TNFα. Downstream of the glucocorticoid receptors NFκB regulates the production of cytokines such as IL-2, IFNα and TNFα. The influence of TNFα on the glucocorticoid receptors

can result in a positive feedback loop and a continuous production of cytokines[72,73] which might result in deregulation of the 24-hour circadian rhythm. Supporting this deregulation at the level of the suprachiasmatic nucleus is the change in the cortisol curve in patients with CRF, as is described by Bower *et al*.[74] Cortisol levels follow a daily curve with a peak in the early morning and a down slope during the day. Bower *et al* have found that breast cancer survivors who suffer from fatigue have a more flattened cortisol slope throughout the day and a significantly elevated cortisol level in the late evening compared to non-fatigued breast cancer survivors.[74]

Serotonin

Serotonin and its receptors influence each other and the HPA-axis. Serotonin (5-hydroxy thryptophan, 5-HT) is made in the pre-synaptic neuron from thryptophan. Its production is regulated by indolamine 2,3 dioxygenase (IDO) which breaks down thryptophan into kynurenine. The activity of IDO is influenced by cytokines, such as IL-2, IL-6 and TNFα.[73]

Once serotonin is released into the synaptic space it activates the post-synaptic neuron and re-uptake by the pre-synaptic neuron. Both processes are regulated by the HT-1a receptors. High levels of serotonin in the synaptic space cause an up regulation of the HT-1a receptors.

There are multiple hypotheses on how serotonin may influence CRF. The most straight forward hypothesis is that lower serotonin levels result in a decreased stimulation of the HT-1a receptors in the hypothalamus, and thereby in a decreased activity of the HPA axis resulting in lower cortisol levels.[75] A second hypothesis suggests that persisting high levels of serotonin, or increased activity of the HT-1a receptors in the hypothalamus, cause a change in the metabolism of the HPA axis, which leads to lower cortisol levels. This increased activity of the HT-1a receptors could be triggered by high levels of IL-1β and TNFα.[7,58,59] The third theory, proposed by Jager *et al*, is that the relationship between serotonin levels and fatigue is U-shaped. This means that both a decrease and an increase in serotonin levels result in a lower cortisol level and thereby fatigue.[76]

Morrow *et al*, and Roscoe *et al* have performed two randomized clinical trials using paroxetine, a selective serotonin reuptake inhibitor (SSRI), in an effort to reduce fatigue during chemotherapy treatment. Both studies show improvement of depressive symptoms, but not in fatigue. These results suggest that correction of the serotonin level does not influence fatigue.[7,8] This might be due to downstream changes that have already occurred at the moment patients start treatment, but one should realize that the evidence for the involvement of serotonin in CRF is only circumstantial.

Other hormones

Other hormones that influence the activity of the HPA-axis are androgens. Shafqat *et al* show in their study that patients with cancer who suffer from fatigue have lower levels of testosterone and dehydroepiandrosteron (DHEA).[77] In patients treated with interferon, which causes fatigue in 70 percent of the patients treated, chronic inhibition of the HPA axis is seen, also resulting in lower levels of estrogen, progesterone and testosterone. Treatment with interferon can also cause a decrease in growth hormone activity. All of these hormone deficiencies are associated with fatigue in otherwise healthy people, meaning that they also can contribute to CRF.[78]

Cytokines

Both malignancy and its treatment are associated with a rise of cytokine levels in plasma.[58,59] The presence of pro-inflammatory cytokines like IL-1, IL-6 and TNFα is found in the microenvironment of tumors.[59,60] Wieseler-Frank *et al* found that, besides tumor cells, glia cells within the central nerve system can also produces cytokines in response to stress.[79] These cytokines can contribute to CRF by their role in the development of anemia, cachexia, anorexia and depression,[59,80] but also by the direct influence they have on the functioning of the HPA-axis. In addition to aberrant expression, Collado-Hidalgo *et al* and Bower *et al* have found three single nucleotide polymorphisms (SNPs) in patients with severe fatigue after curative treatment for breast cancer in the genes encoding IL-1β, IL-6 and TNFα as a potential underlying mechanism of CRF.[81,82] Bower *et al* also show that increasing numbers of high expression alleles predict fatigue severity, this might explain some of the differences in fatigue levels between patients.[82]

TREATMENT OF CRF

Adequate treatment of CRF starts with identifying factors that contribute to this fatigue. A fatigue history should cover its severity, pattern, contributing and relieving factors and the impact it has on daily functioning. Patients complaining of fatigue should also be assessed for depressive symptoms. Laboratory analysis can help to diagnose or rule out anemia, electrolyte imbalance and vitamin or hormonal deficiencies. The extent to which contributing factors are studied should be in line with the patient's current condition and prognosis.

The NCCN fatigue guideline identifies seven factors which may contribute to CRF. These factors are pain, emotional distress, sleep disturbance, anemia, nutritional deficiencies, decreased condition and co-morbidities.[3] All of these contributing factors influence the aforementioned pathophysiological mechanisms, e.g. pain causes serotonin release and nutritional deficiencies might hamper ATP regeneration. Especially anemia has been studied extensively as a treatable cause of fatigue in patients with cancer. The current standard is to treat these patients with red blood cell transfusion or with erythropoiesis stimulating agents until the hemoglobin level is high enough to avoid transfusion.[3] There are, however, some safety concerns for erythropoiesis stimulating agents in patients with cancer, as they may increase the risk at thrombo-embolism.[83] Treatment of anemia may alleviate fatigue on short term, but the study of Mercante *et al*. shows that this effect has subsided at day 15 after transfusion, even though hemoglobin levels remain adequate.[84]

In general the specific cause of CRF is difficult to identify in a particular patient and its cause is expected to be multifactorial but primarily due to the biological activity of the progressive disease and the severity of the treatment. Both pharmacological and non-pharmacological interventions can be applied to reduce CRF. A flow chart for treatment of CRF is provided by the NCCN guideline and summarized in figure 2,[3] but none of these interventions have a high chance to reduce CRF. Therefore, we advocate to be very restrictive with pharmacological interventions, because these interventions may lead to subsequent treatment induced toxicity.

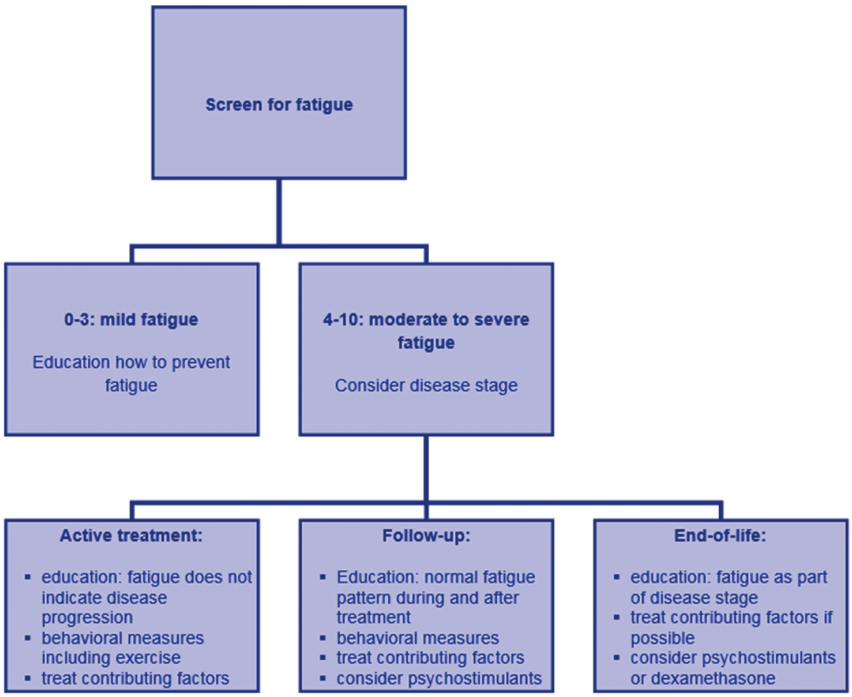

Figure 2. Summary NCCN guideline. The NCCN guideline on cancer related fatigue advices to ask patients to rate their fatigue on a scale from 0 to 10.[3] Further advice is given considering fatigue score and disease stage.

Non-pharmacological treatment

Examples of non-pharmacological interventions in fatigue are patient education, fatigue diaries, sleep hygiene measures, cognitive behavioral therapy, and exercise.[1,3,85-87] Many patients try to reduce fatigue by resting, but this often does not restore energy and might even worsen fatigue in the long term.[1,88,89] Many practitioners advise sleep hygiene measures to patients suffering from CRF. These measures focus on establishing a regular sleep pattern by performing activities during the day, and avoidance of stimulants before and during the night.[90-92] Although these measures are often advised, there is little evidence for their efficacy.[90-92]

Cognitive behavioral therapy

Another type of a non-pharmacological intervention is cognitive behavioral therapy. A systematic review performed in 2009 indicated that in four out of five randomized clinical trials (RCT), psychological interventions based on cognitive behavioral therapy specifically aimed at reducing fatigue were effective in reducing fatigue during cancer treatment.[93] In all of these RCTs, patients received education about fatigue, learned self-care or coping techniques, and how to balance activities and rest.[93] A critical note in this review is that follow up measurements performed in these studies might indicate that the beneficial effect on fatigue subsides after the study intervention has ended.

Exercise

A number of trials have proven exercise as an effective non-pharmacological method to reduce fatigue in an out-patient setting.[86,94-100] However, some of these trials are difficult to interpret because they lack proper randomization or placebo intervention.[94] Overall, Cramp et al found a standardized mean difference of -0.27 (95% CI -0.37 to -0.17) in favor of exercise in their systematic review.[98] At the moment, there is no clear evidence on what type of exercise is the most effective, either low intensity, like walking, or high intensity training.[98] In the PACES-trial, which is currently ongoing, this question is addressed.[101] Most studies on exercise in cancer patients are performed in curative treatment settings. Although only a few small studies were conducted in palliative care patients, these also revealed reduced fatigue levels in the intervention group.[85]

Pharmacological treatment

Pharmacological treatment of primary CRF can have multiple entry-points, such as reducing cytokine-load by inhibition of the immune response, restoring peripheral energy depletion, and treating metabolic disorders.[1,102] Anticancer treatment can both alleviate fatigue by decreasing tumor burden, but can also cause fatigue as a side effect. Most treatment options mentioned in palliative care guidelines are, however, symptomatically, with for example activating agents like dexamphetamine, (dex-)methylphenidate and modafinil.

To find pharmacological treatment options for CRF a Medline search was performed. Details and results of this search can be found in supplement 2. Drugs that were studied for their effect on CRF were bupropion,[103] (L-)carnitine,[104,118] dexamphetamine,[105] dex-methylphenidate,[106,107] donepezil,[108] etanercept,[109] infliximab,[110] methylphenidate,[15,111-115,120] modafinil,[2,116] paroxetine,[7,8] and thyrotropin releasing hormone.[117] Most drugs were not compared to a placebo or did not show significant benefit compared to a placebo (see figure 3).[7,8,103-118] One drug, methylphenidate, showed promising results,[111-113,119] but in the latest and largest trials no improvement of fatigue by this treatment was found compared to placebo.[114,120,121] A variant on this drug, dexmethylphenidate, showed an improvement of fatigue compared to placebo in the trial by Lower et al, but also had noticeable side effects.[122] In a subgroup analysis of one of the larger placebo-controlled trials, modafinil had significantly better effect on fatigue than the placebo. This subgroup consisted of patients with severe fatigue at baseline (72.6% of the total study group).[2] Effect size in this study that compared modafinil to placebo in 867 patients was small (-.50 points on a 10 point scale for modafinil, compared to -.33 for placebo in the whole group (P .08) and -1.31 for modafinil compared to -0.87 for placebo in the severely fatigued patients (P 0.033)). This might be partly due to the in parallel start of treatment with chemotherapy.

Steroids, such as dexamethasone and prednisone, are often recommended in guidelines for CRF in the terminal stage.[3] This recommendation is based on clinical experience, supported by three studies in which fatigue is not an endpoint, but overall quality of life improved during treatment with steroids.[123-125] There has no randomized controlled trial been published on steroids with CRF as endpoint. The effect of steroids on multiple contributing factors to fatigue seems a strong argument for their potential efficacy. However, detrimental side effects of long-term

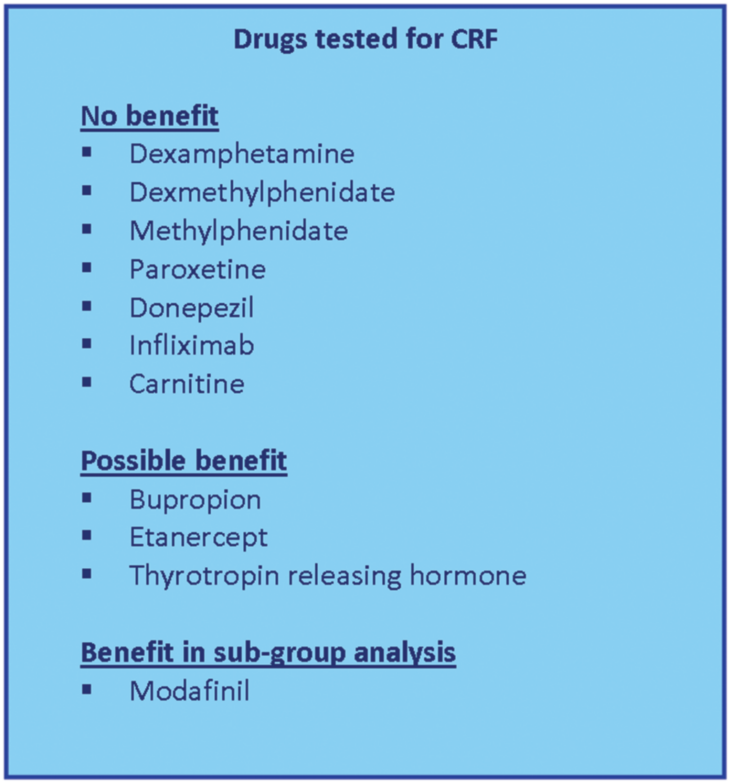

Figure 3. Drugs tested for CRF. This figure summarizes the results of the studies listed in supplement 2 into three categories: drugs showing no benefit over placebo, drugs showing positive effect in small studies which need to be confirmed in larger, placebo-controlled trials and one drug that showed some benefit over placebo in such a trial.

corticosteroids use are well known, and therefore this treatment approach should be avoided in general.

Sleeping agents

Sleeping agents are frequently used to treat fatigued patients suffering from insomnia. They often have adverse effects or even paradoxical impact on sleep disturbance, especially in the elderly patient, and are therefore not recommended for treatment of CRF.[90,126] Melatonin agonists do not seem to have this adverse effect and can be considered as a sleeping agent for patients with insomnia, but have not yet been evaluated for their specific effects on CRF.[90] Lissoni *et al* have performed a number of trials to study the effects of melatonin on cancer progression and treatment side effects. They did find an effect of melatonin on fatigue as a treatment-related side effect, but a placebo-effect cannot be ruled out.[127-131]

Possible future interests for pharmacological treatment of CRF

Taking into account the likely role of cytokines in the pathophysiology of fatigue, drugs targeting excessive cytokine release, such as cyclo-oxygenase-2 (COX-2) inhibitors and NSAIDs, could be evaluated for their effect on CRF. Also α-melanocyte-stimulating hormone (α-MSH), a pituitary neuropeptide that functions as a mood-elevating substance and is known to inhibit certain pro-inflammatory activities of cytokines,[132,133] could be studied for its effect on CRF.

Complementary or Alternative medicine

Chinese herbal medicine and other complementary therapies are frequently used by patients beside their normal treatment. Traditional Chinese medicine is often plant or herb based, sometimes complemented with minerals.[134] Although there are many articles applauding its effect, most of these studies have poor quality because of limited power, no comparison to placebo or inadequate blinding. Among trials specifically studying the effects of complementary therapies on CRF, positive effects are found for bojungikki-tang, which consists of ten different plant extracts among which a considerable amount of ginseng.[135] Barton et al, who studied different dose levels of American Ginseng, did seem to find a dose-response relationship. However, the primary aim of the trial was not met, and results did not reach significance.[136] Another trial that studied the effects of ginseng, had major inclusion problems because of safety issues that can occur when ginseng is combined with other drugs.[137]

Complementary therapies do not only include oral treatment. Examples of other treatments are acupuncture and yoga. A review performed by Posadzki *et al* showed inconclusive results for acupuncture trials, which were of variable quality.[138] This review did however not include the study performed by Molassiotis *et al*, that showed positive results, but could not rule out a placebo effect.[139] Yoga is increasingly often practiced in Western countries and can be viewed as a type of low intensity exercise. In a systematic review of the possible physical and psychosocial effects of yoga in cancer patients Buffart *et al* found that yoga resulted in a moderate reduction of fatigue (d=-0.51) but also mentions that the current evidence is insufficient to draw firm conclusions on the clinical implications.[140]

For clinical practice the lack of evidence regarding the effects of the different complementary therapies implicates that patient requests and questions about this subject should be handled with care, whilst keeping in mind the possible interactions with other treatments.

SUMMARY

CRF is a common problem for patients with cancer, both during and after treatment. It is disproportionate to physical activities, usually more severe than fatigue in healthy people, and has a negative influence on daily activities and quality of life. The EORTC QLQ-C30 fatigue subscale, the FACT-F and the FQ are most frequently used and best validated methods to clinically assess CRF. In the clinical setting most patients are being asked to rate their fatigue on a scale from 0 to 10, with 4 or higher as a cut-off point to take further action.[3]

Factors that may have a potential influence on CRF include physical and mental factors. With regard to the latter, changes in the levels of cortisol, serotonin, and several cytokines may have detrimental effects on the function of the hypothalamus and suprachiasmatic nucleus possibly causing or increasing CRF.

Treatment of CRF starts with identification and treatment of possible contributing factors, like anemia. When there are no solvable factors involved, symptomatic treatment should be applied. Currently, this should mainly consist of supportive cognitive therapy, exercise programs, while pharmacological treatment should be avoided as much as possible, because of low success rate to respond favorably while potentially toxic. Modafinil is the only drug studied in CRF showing a possible benefit over placebo in a subgroup of patients with severe fatigue before starting chemotherapy treatment.

In future studies on CRF pharmacological agents to alleviate fatigue in palliative care patients who cannot participate in exercise programs should be evaluated. Agents suggested for future studies are agents that influence cytokine production, such as acetylsalicic acid, as they show promising results in fatigued patients with other diseases.

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SUPPLEMENTARY DATA

Supplementary table 1. Fatigue questionnaires. There are many questionnaires developed to assess fatigue or specifically cancer related fatigue. Questionnaires listed below focus specifically on fatigue and are available in English. Properties mentioned of each questionnaire give an impression of the length and possible results together with its validity.

Questionnaire -abbreviation -	No. of items (subscales)	Response scale	Results (cut-off point) [1]	Recall period
Brief Fatigue Inventory - BFI -[12,17,20]	9 (1)	11-point Likert	0-10 (0=no fatigue, 1-3=mild,4-6=moderate,7-10=severe)	24hr
EORTC QLQ-C30 fatigue subscale [12,23]	3 (1)	4-point Likert	0-100	24hr-1week
Fatigue Questionnaire - FQ – [20,27,54]	11 (2)	4-point Likert	0-33 (≥29 for chronic fatigue syndrome) (alternative scoring system: 0-11, cut-off ≥4)	Present time
Functional assessment of cancer therapy for fatigue - FACT-F -[12,20,31,54]	13 (1)	5-point Likert	0-52 points	1 week
Rhoten Fatigue Scale - RFS - [12,20,46]	1 (1)	11-point Likert	0-10	Present time

[1] Higher scores correlate to higher fatigue levels unless mentioned otherwise
[2] Not assessed

Supplementary table 2. Drugs studied for CRF. A Medline search was performed in February 2013 using MeSH terms: 'fatigue' 'neoplasms' and 'drug therapy'. 622 results were screened by title and abstract for their relevancy. Reference lists were screened to find missing data. Included studies focus on fatigue in patients with cancer, not caused by anemia.[2,7,8,15,103-118,120-122]

Drug	Study	Patient group	Intervention	Control
Bupropion	Cullum 2004	Cancer, assessed for psychiatric disorder, fatigued > depressed	Bupropion SR100 to 300 dosed on response	-
Carnitine	Cruciani 2006	Advanced cancer, carnitine deficient	L-carnitine 250 to 3000 mg/day	-
	Cruciani 2012	Cancer and self reported fatigue	L-carinitine 1000mg twice daily	Placebo

	Tested in cancer patients	Internal consistency	Test-retest reliability	Sensitivity to Change	Advantages according to developers or validation studies	Disadvantages according to validation studies
	Yes	0.96	0.90	Yes	Simple language	
	Yes	>0.80	0.63	Yes	Translated and validated in many languages. Validated in >5000 patients	Focuses on physical fatigue
	Yes	0.88-0.91	-[2]	Yes	Easy to understand and quickly answered	
	Yes	0.93-0.95	0.72-0.90	Yes	Translated and validated in many languages. Validated in >5000 patients	
	Yes	0.62-0.74	-	-	Easy to administer	Only useful for screening

	Sample size	Measurement method[1]	Effectsize[1]	Conclusion
	15	Patient assessment: fatigue much worse- much improved	13 of 15 subjects reported improvement, 1 felt much worse	Bupropion treatment can be an alternative to currently available treatment. Placebo controlled studies necessary.
	27	BFI + side effects	BFI: 66.1 ± 12 to 39.7 ± 26 (P < .001) Side effects: mild nausea	L-carnitine is well tolerated and improves fatigue in deficient patients. Placebo effect could not be ruled out.
	189 v. 187	BFI + FACT-F	BFI -0.96 vs -1.11 (P = .57)	This approach for L-carnitine supplementation lacks efficacy.

Supplementary table 2. (continued)

Drug	Study	Patient group	Intervention	Control
Dexamphetamine	Auret 2009	Advanced cancer, fatigue ≥4 on a scale from 0 to 10, no current chemotherapy	Dexamphetamine 10mg twice daily	Placebo
Dex-methylphenidate (d-MPH)	Butler 2007	Metastatic brain tumor or primary brain tumor starting RT to the brain	d-MPH 5-15mg twice daily	Placebo
	Mar Fan 2008	Breast cancer during adjuvant chemotherapy	d-MPH 5-10mg	Placebo
	Lower 2009	Cancer diagnosis ≥ 2 months after chemotherapy, ICD-10 Criteria for CRF	d-MPH 10-70mg twice daily	Placebo
Donepezil	Bruera 2007	Advanced cancer, fatigue score ≥4 on a scale from 0 to 10	Donepezil 5mg	Placebo
Etanercept	Monk 2006	Advanced cancer, refractory to conventional therapy	Docetaxel 43mg/m2 + Etanercept 25mg s.c. 2xper week	Docetaxel 43mg/m2
Infliximab	Tookman 2008	Advanced cancer, not receiving chemo-, immuno- or radiotherapy. FSS ≥ 42.	Infliximab 5 mg/kg	-
Methylphenidate	Sugawara 2002	Advanced cancer, referred to psychiatrist for fatigue	Methylphenidate 5 to 30mg/ day by clinical judgment	-
	Schwartz 2002	Melanoma patients starting INF-α treatment	Methylphenidate SR 20mg + exercise program 15-30 min 4 days a week	Historical controls: no methylphenidate nor exercise program
	Bruera 2003	Advanced cancer, fatigue ≥4 on a scale of 0 to 10	Methylphenidate 5mg/2hr max. 20mg/24hr	-

Sample size	Measurement method[1]	Effectsize[1]	Conclusion
25 v. 25	BFI	BFI: 5.3 v. 5.8 to 5.0 v 5.1 on day 8 (P = .414)	Dexamphetamine 10mg twice daily does not improve fatigue.
34 v. 34	FACT-F	FACT-F 34.0 ± 10.4 to 33.7 ±2.3 v. 35.6 ±2.5 (P = .64)	This trial did not demonstrate an advantage for prophylactic d-MPH on fatigue.
19 v. 28	FACT-F	FACT-F: 38 to 38 for d-MPH, 37 to 38 for placebo (P = .31)	No significant benefit was demonstrated.
75 v. 77	FACT-F	FACT-F change: -10.5 v -6.8 (P = .02)	D-MPH can be of benefit in a select group of patients
71 v. 71	FACT-F + ESAS	FACT-F: 19.2 to 28.7 v. 30.3 (P = .57) ESAS: 7.3 to 6.1 v. 5.9 (P = .18)	Donepezil is not superior to placebo in the treatment of CRF.
6 v. 6 patients	Docetaxel dose intensity + NCI CTC version 2 + FSI weekly	Docetaxel dose intensity improved whit etanercept (29 v 35 of 36 intended doses P .055) + FSI score rose less whit etanercept during therapy (p < .001)	Findings of this pilot study encourage further exploration of TNF blockade. A larger study with predetermined end points for fatigue and placebo control arm is required.
17	FSS	6/17 showed some improvement of FSS score	The results of this study do not show an overall improvement of fatigue.
16	VAS-F	VAS-F 77 (±15) to 54 (±28) (P = .01)	Methylphenidate may be useful for alleviating CRF.
12 (8 M+E, 4 only exercised) v. 16	SCFS + SF-36	SCFS and SF-36 scores showed less increased fatigue for the exercise group than the control group, and even less increase for the methylphenidate + exercise group.	Methylphenidate in combination with exercise might minimalise fatigue as a dose-limiting side effect of INF-α.
31	Fatigue on a 0 to 10 scale + FACT-F + Edmonton Symptom Assessment Score (ESAS)	0 to10: 7.2 ± 1.6 at baseline to 4.4 ± 3.1 after 1 week (P < .0001) + FACT-F fatigue subscale 17.5 ±11.3 to 31.9 ±17.9 (P < .0001) + ESAS fatigue subscale 7.2 to 3.0 (P < .001)	Methylphenidate improves fatigue, although placebo effect is not ruled out.

Supplementary table 2. (continued)

Drug	Study	Patient group	Intervention	Control
	Bruera 2006	Advanced cancer, fatigue ≥4 on a scale of 0 to 10	Methylphenidate 5mg/2hr max. 20mg/24hr	Placebo
	Roth 2010	Prostate cancer, fatigue ≥ 4 on a scale of 0 to 10	Methylphenidate start at 5mg max 30mg	Placebo
	Johnson 2010	Recurrent gynecologic cancer, reporting fatigue during chemotherapy	Methylphenidate 5-10mg twice daily	-
	Moraska 2010	Cancer patients reporting fatigue ≥4 on a scale of 0 to 10	Methylphenidate 18mg day 1-7, 36mg day 8-14, 54mg day 15-28	Placebo
	Buera 2013	Patients with advanced cancer reporting fatigue ≥4 on a scale of 0 to 10	Methylphenidate start at 5mg max 20 mg ± Nursing telephone intervention	Placebo ± Nursing telephone intervention
Modafinil	Spathis 2009	Non Small Cell Lung Cancer, fatigue ≥4 on a scale of 0 to 10, no chemo or radio therapy	Modafinil 100mg day 1 to 7, 200mg day 8-14.	-
	Jean-Pierre 2010	Cancer, planned to start at least 4 cycles of chemo therapy, BFI question3 ≥2 after cyle 2 (baseline).	Modafinil 100mg	Placebo
Paroxetine	Morrow 2003	Cancer patients about to start at least 4 chemo therapy cycles, who report fatigue MAF question 1>1 after the second cycle.	Paroxetine 20mg	Placebo
	Roscoe 2005	Breast cancer patients on chemo therapy, not radiotherapy	Paroxetine 20mg	Placebo
Thyrotropin-Releasing Hormone	Kamath 2009	Breast cancer patients with cancer related fatigue according to ICD-10 criteria and FACT-F < 34	TRH 0.5mg and 1.5mg alternated with placebo	Placebo

	Sample size	Measurement method[1]	Effectsize[1]	Conclusion
	56 v. 56	FACT-F + ESAS fatigue score (scale 0-10)	FACT-F 17.0 to 26.6 v. 24.5 (P = .31) ESAS 7.4 to 4.7 v. 5.5(P = .14)	Methylphenidate is not superior to placebo though both groups showed significant improvement of fatigue.
	16 v. 16	BFI + FSS	BFI: 5.13 v 4.01 to 2.19 v. 2.76 (P = .07) FSS: 4.27 to 3.54 v 3.68 (P = .78)	Methylphenidate seems to have some effect, although there are some side effects.
	32	FSI	FSI baseline – week 8: 84.7 (±21.2) to 57.2 (±30.8) (P = .0001)	Methylphenidate is beneficial for women with recurrent gynecologic cancer, however placebo controlled trial is necessary.
	74 v. 74	BFI + SF-36 vitality subscale + Pittsburgh Sleep Quality Index	'No significant difference between methylphenidate and placebo arms' (P = .32)	The results of this trial are unable to support the hypothesis that methylphenidate would be an effective therapy for the management of CRF.
	47+45 v. 48+50	FACT-F + ESAS Fatigue Score	FACT-F change 5.50 v. 6.00 (P = .69) ESAS FS change -2.00 v. -2.00 (P = .86)	Fatigue scores improved in all study groups, no differences between groups
	20	FACT-F + FQ + ESS + HADS	FACT-F 17 to 7 (P = .001) + FQ change -10.0 (P < .0001) + ESS 10 to 5 (P = .005) + HADS 18 to 14.5 (P = .041)	Modafinil may have a clinically significant effect on fatigue, a randomized controlled trial is feasible.
	431 v. 436	BFI question3 + ESS	BFI-3: 7.39 to 6.87 v. 7.43 to 7.09 + ESS: 18.16 to 16.82 v. 19.19 to 18.38 (all P values < .05)	Modafinil seems to be a promising agent to diminish CRF.
	277 v. 272	FQ + MAF + POMS-F	FQ cycle 4: 52.3 v 53.8 (P = .40) + MAF c4: 5.5 v. 5.4 (P = .76) + POMS-F c4: 7.7 v. 8.4 (P = .18)	Paroxetine had neither beneficial nor detrimental effects on fatigue.
	59 v. 63	FQ + MAF + POMS-F	FQ cycle 4: 44.6 v. 48.0 + MAF c4: 4.6 v. 5.0 + POMS-F c4: 6.0 v. 7.1 (P > .27 for all scales)	Paroxetine did reduce depression but not fatigue.
	3 (cross-over)	VAS-Energy	Change from baseline >25% in 4 out of 6 TRH infusions and 1 out of 6 saline infusions	TRH seems to have an effect on fatigue, more data are needed.

8

MUSCLE MASS AS A TARGET TO REDUCE FATIGUE IN PATIENTS WITH ADVANCED CANCER

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ABSTRACT

Background

Cancer related fatigue (CRF) reduces quality of life and the activity level of patients with cancer. CRF can be reduced by exercise interventions that may concurrently increase muscle mass. We hypothesized that low muscle mass is directly related to higher CRF.

Methods

233 patients with advanced cancer starting palliative chemotherapy for lung, colorectal, breast, or prostate cancer were studied. The skeletal muscle index (SMI) was calculated as the patient's muscle mass on level L3 or T4 of a computed tomography (CT-scan), adjusted for height. Fatigue was assessed with the Functional Assessment of Chronic Illness Therapy(FACIT)-fatigue questionnaire (cut-off for fatigue <34). Multiple linear regression analyses were conducted to study the association between SMI and CRF adjusting for relevant confounders.

Results

In this group of patients with advanced cancer, the median fatigue score was 36 (IQR 26-44). A higher SMI on level L3 was significantly associated with less CRF for men (B 0.447, p 0.004) but not for women (B -0.401, p 0.090). No association between SMI on level T4 and the FACIT-fatigue score was found (n=82).

Conclusions

The association between SMI and CRF may lead to the suggestion that male patients may be able to reduce fatigue by exercise interventions aiming at an increased muscle mass. In women with advanced cancer, CRF is more influenced by other causes, because it is not significantly related to muscle mass. To further reduce CRF in both men and women with cancer, multifactorial assessments need to be performed in order to develop effective treatment strategies.

INTRODUCTION

Cancer related fatigue (CRF) is characterized by significant physical, emotional and/or cognitive exhaustion, which is disproportionate to the activity level and interferes with usual functioning in patients with cancer.[1] CRF is one of the most prevalent symptoms experienced by patients with cancer, both during and after treatment.[2,3] Although advances are being made, the etiology of CRF is not yet fully understood, and treatment is mostly symptomatic.[4,5] The pathophysiology of CRF is determined by central and peripheral aspects of fatigue.[4,6,7] Pro-inflammatory effects of cancer result in direct changes in the muscle metabolism, leading to reduced ATP levels, reduced protein synthesis, and localized electrolyte imbalances causing peripheral CRF.[6] Central effects of elevated cytokine levels (among which IL-2, IL-6 and TNFα) cause changes in activity of the hypothalamus-pituitary-adrenal axis, leading to a sensation of reduced capacity to perform physical work, but also to a reduced androgen expression.[6,8] Both pathways could result in a loss of muscle mass, but whether a decreased muscle mass itself affects CRF is unclear.[4,9]

Promising results for the treatment of CRF are seen with exercise interventions.[10-12] Exercise interventions can improve muscle mass, strength, and functioning, depending on the type and intensity of exercise. Which type of exercise (e.g. aerobic, resistance), and at which intensity level, contributes most to the positive effect on CRF is not yet fully known[4,12,13] and neither is the pathophysiological mechanism of this effect. Several studies have been performed investigating the effect of exercise interventions on CRF in patients with limited disease, and their results indicate improvement of CRF and increased muscle mass, but the effect sizes varied.[14-18] In these trials the association between muscle mass and CRF was not studied. Current data on the association between muscle mass and CRF are scarce and conflicting.[19,20]

In this study we aim to accurately define to what extent muscle mass is related to CRF in patients with advanced cancer. We performed a cross-sectional study of the association between muscle mass and CRF in patients with advanced cancer. A direct relation between muscle mass and CRF, would further support the hypothesis that improving muscle mass is an important target for reducing CRF.

METHODS

A cross-sectional study was performed in patients with advanced cancer scheduled for treatment with chemotherapy between June 2011 and July 2014. This study was embedded in a large observational study in patients with advanced cancer (Netherlands trial register NTR3094), which resulted in two publications.[21,22] Patients with colorectal, breast, prostate, or lung cancer, normal blood counts, and no chemistry abnormalities who were scheduled to start a new line of chemotherapy were included in this trial. Exclusion criteria were peripheral edema or ascites, chemotherapy in the previous month, pregnancy, and insufficient comprehension of the Dutch language to complete questionnaires. After providing informed consent, patient characteristics and data on comorbidity and prior treatments were collected from the patients' medical files. All data were anonymized and stored in the web-based database system Open Clinica (version 3.3). This observational study was approved by the ethics committee of the VU University medical center.

Assessments

Fatigue was assessed with the FACIT-fatigue.[23] The FACIT-fatigue is a validated questionnaire focusing on physical fatigue and the functional consequences of fatigue. It has an excellent internal consistency (Cronbach's alpha 0.93-0.95) and good test-retest reliability (*r* 0.72-0.90).[23-25] The thirteen items are scored on a 4-point Likert scale, resulting in a total score between 0 and 52 points, with lower scores indicating higher levels of CRF. A score <34 on the FACIT-fatigue was previously defined as a cut-off for fatigue.[26,27] This cut-off is concordant with the ICD-10 criteria for CRF which state that significant fatigue, diminished energy and an increased need to rest (disproportionate to any recent change in activity level) should be present during at least two consecutive weeks in the past month, or that one or two of these symptoms are present combined with 5 or more out of 10 other symptoms that directly influence daily activities.[27]

Skeletal muscle area (cm^2) was measured with SliceOmatic Software V 5.0 (Tomovision, Magog, Canada) using routine CT scans conducted for diagnostic purposes before start of chemotherapy treatment. The third lumbar vertebra (L3) was used as a standard landmark.[28,29] The first image extending from L3 to the iliac crest was chosen to measure total muscle cross-sectional area. The L3 region contains psoas, para-spinal muscles (erector spinae, quadratus lumborum), and the abdominal wall muscles (transversus abdominus, external and internal obliques, rectus abdominus). These muscles were identified based on their anatomic features by a trained researcher. The structures of those specific muscles were quantified based on pre-established thresholds of Hounsfield Units (HU) (-29 to + 150) of skeletal muscle tissue.[30] Cross-sectional areas (cm^2) of the sum of all these muscles were computed by summing tissue pixels and multiplying by the pixel surface area. In patients with lung cancer no routine CT-scan of the abdomen including L3 are being made. Therefore, there were no CT images available on level L3 for the lung cancer patients, T4 was used as an alternative for the assessment of the skeletal muscle area. This region contains pectoral muscles, external intercostal, serratus anterior, teres major, subscapularis, infraspinatus, rhomboid major, erector spinae and trapezius muscles. Measurements at the T4 level are currently being validated, therefore these results were analyzed separately and should be interpreted with caution.

Skeletal Muscle Index (SMI) was calculated as the ratio of skeletal muscle area (cm^2)/height $(m)^2$. Body height was measured using a stadiometer; the patient was standing barefoot and height was determined to the nearest cm. Low SMI on level L3 was defined as <41cm^2/m^2 for women; <43 cm^2/m^2 for men with a body mass index (BMI) <25 kg/m^2; and <53 cm^2/m^2 for men with BMI ≥25 kg/m^2.[31] For level T4 no reference values are available.

Statistical analysis

Descriptive results are presented by their mean and standard deviation (SD), or median and interquartile range (IQR) whenever appropriate. Univariate and multiple linear regression were used study the association between CRF and SMI, adjusted for age; gender; tumor type; chemotherapy treatment line (first vs. second and higher); Charlson Comorbidity Index; and chemotherapy, hormone therapy, targeted therapy, or high dose corticosteroid treatment (equivalent to prednisone >10mg/day over 3 weeks) in the past six months. These factors were chosen as they

may influence CRF and/or SMI.[32,33] To study whether the association between SMI and fatigue was modified by age, gender and hormone therapy we added the interaction terms of SMI with these variables into the regression equation. All statistical tests were 2-sided, and $p<0.05$ was considered statistically significant. Analyses were performed with IBM SPSS version 22.0.0.0 (IBM, Armonk, NY, USA).

RESULTS

In total, 302 patients were included, of whom 233 patients had both completed the FACIT-fatigue questionnaire and had a CT-scan that met the required conditions for assessment of the skeletal muscle area (Figure 1). The L3 group (n=151) comprised patients with colorectal, prostate and breast cancer. The T4 group (n=82) comprised patients with lung cancer. Patients were included with a CT scan within 90 days of their assessment, however approximately 80% of the patients had a CT scan made within the last 30 days as was considered appropriate for their cancer treatment by their oncologist. The median number of days between the CT scan and FACIT-fatigue scoring was 15 days (IQR 7-28). Patient characteristics are shown in Table 1.

The median score on the FACIT-fatigue questionnaire was 36 (IQR 26-44), 96 patients (41%) were diagnosed with CRF (FACIT-fatigue score <34, Table 2). The median SMI was 43 cm^2/m^2 in the L3 group and 59 cm^2/m^2 in the T4 group (Table 2). In the L3 group 58% of the men and 61% of the women had a low SMI.

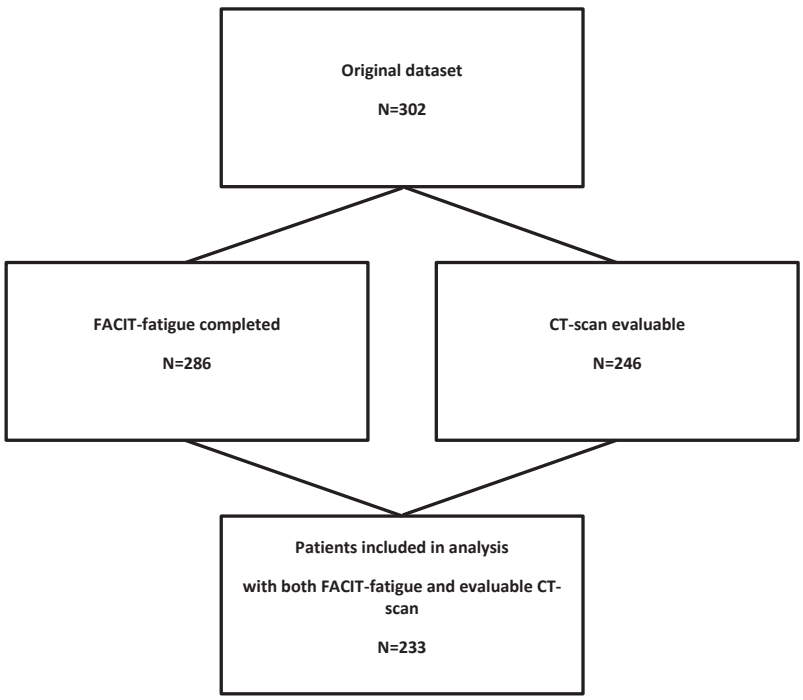

Figure 1. Study flow chart.

Table 1. Patient characteristics.

		All patients n=233 n (%)	L3 group n=151 n (%)	T4 group n=82 n (%)
Age	mean (SD)	63.6 (9.9)	64.5 (9.8)	61.9 (9.9)
Gender	male	129 (55)	89 (59)	40 (49)
	female	104 (45)	62 (41)	42 (51)
Cancer type	lung	82 (35)	-	82 (100)
	colorectal	75 (32)	75 (50)	-
	prostate	44 (19)	44 (29)	-
	breast	32 (14)	32 (21)	-
Brain metastasis		18 (8)	3 (2)	15 (18)
Chemotherapy in past 6 months		35 (15)	26 (17)	9 (11)
Radiotherapy in past 6 months		9 (4)	3 (2)	6 (7)
Hormone therapy in past 6 months		31 (13)	31 (21)	0 (0)
Targeted therapy in past 6 months		18 (8)	14 (9)	4 (5)
Corticosteroid use in past 6 months[1]		24 (10)	16 (11)	8 (10)
ECOG performance status	0	57 (25)	46 (31)	11 (13)
	1	94 (40)	83 (55)	11 (13)
	2	17 (7)	14 (9)	3 (4)
	unknown	65 (28)	8 (5)	57 (70)
Charlson Comorbidity Index[2]	0	165 (71)	112 (74)	53 (65)
	1-2	62 (27)	35 (23)	27 (33)
	3-4	4 (2)	3 (2)	1 (1)
	≥5	2 (1)	1 (1)	1 (1)
Chemotherapy line	1st	183 (79)	114 (76)	69 (84)
	2nd	32 (14)	24 (16)	8 (10)
	3rd	10 (4)	7 (5)	3 (4)
	>3rd	8 (3)	6 (4)	2 (2)
C-reactive proteine (mg/L)	median (IQR)	12 (4-33)	9 (4-28)	13 (4-35)
Albumin (g/L)	mean (SD)	35 (4)	36 (4)	35 (5)
Haemoglobin (mmol/L)	mean (SD)	8.0 (1.0)	7.9 (1.0)	8.2 (1.0)
Creatinin (µmol/L)	median (IQR)	68 (57-83)	68 (58-83)	70 (59-84)
BMI (kg/m^2)	mean (SD)	25.6 (4.0)	26.2 (3.8)	24.6 (4.1)
BMI males (kg/m^2)	mean (SD)	26.0 (3.7)	26.6 (3.4)	24.7 (4.1)
BMI females (kg/m^2)	mean (SD)	25.1 (4.3)	25.6 (4.3)	24.4 (4.2)

Characteristics of the patients included in the study. BMI= Body Mass Index; ECOG= Eastern Cooperative Oncology Group; IQR = inter quartile range (25th and 75th percentile); SD = standard deviation of the mean.

1. >10mg prednisolon/day for at least 3 weeks

2. Charlson Comorbidity Index, not adjusted for age, primary cancer diagnosis was not counted as comorbidity

The univariate association between SMI and CRF in the L3 group had a B of 0.230 (95% CI -0.004-0.464, p 0.054) (Figure 2 and Table 3). In the multivariate analysis this association was modified by gender ($B_{interaction}$ 0.716, 95% CI 0.172-1.261, p 0.010). Age and hormone therapy did not modify the association between SMI and CRF. Subsequent stratified analysis showed a statistically significant positive association between SMI and CRF in men (B 0.345, 95% CI 0.017-0.672, p 0.039)

Table 2. SMI and FACIT-fatigue scores.

	Skeletal Muscle Area (cm^2) median (IQR)		Skeletal Muscle Index (cm^2/m^2) median (IQR)		FACIT-fatigue score median (IQR)			FACIT-fatigue score <34 n (%)		
CT-level	**T4**	**L3**	**T4**	**L3**	**Overall**	**T4**	**L3**	**Overall**	**T4**	**L3**
Total group T4 n=82 L3 n=151	177 (149-210)	133 (109-153)	59 (53-69)	43 (38-50)	36 (26-44)	35 (23-43)	38 (29-45)	96 (41)	37 (45)	59 (39)
Men T4 n=40 L3 n=89	208 (189-236)	148 (133-167)	67 (59-73)	46 (42-52)	38 (26-45)	33 (21-41)	40 (31-47)	49 (38)	20 (50)	29 (33)
Women T4 n=42 L3 n=62	153 (132-165)	108 (101-124)	55 (51-62)	39 (36-45)	36 (25-43)	37 (25-44)	34 (27-43)	47 (45)	17 (41)	30 (48)

Skeletal muscle data and FACIT-fatigue scores of the patients included in the study. Data are presented for the entire group and separately for patients with a CT-scan on the level of the 3rd lumbar or 4th thoracic vertebrae, and for men and women separately. For the FACIT-fatigue questionnaire a score below 34 points correlates with clinically significant fatigue.

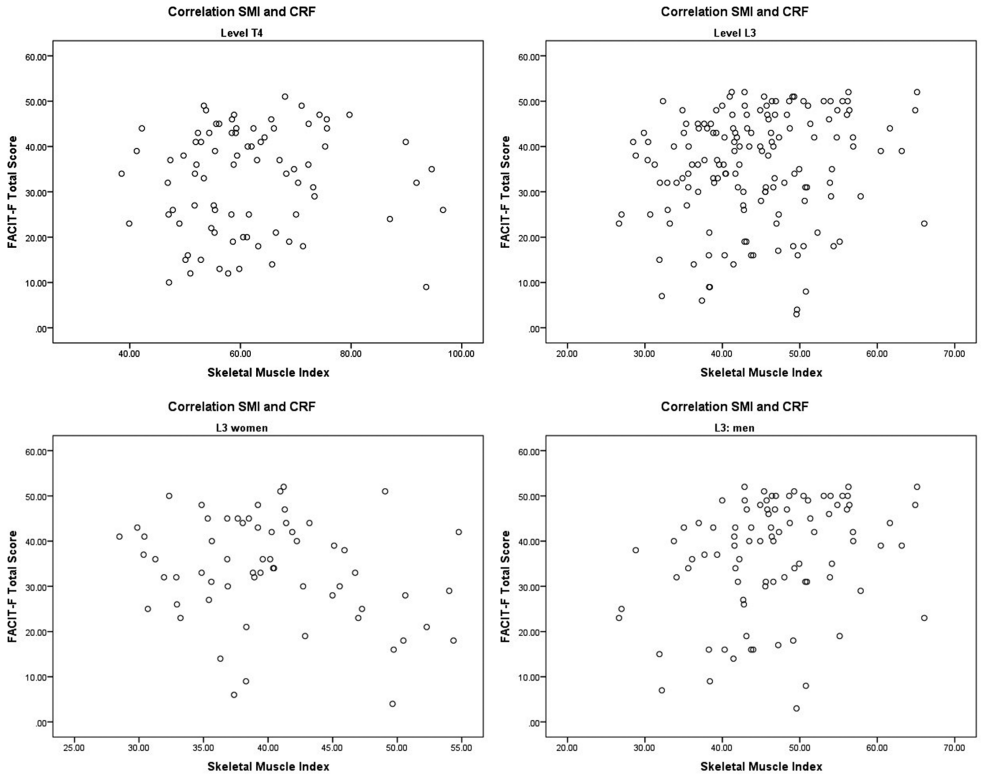

Figure 2. Correlation SMI and FACIT-fatigue. Scatter plots of skeletal muscle index (SMI) measured with CT-scan on the level of vertebra T4 or L3, and cancer related fatigue (CRF) measured with the FACIT-fatigue questionnaire. In the T4 group no association was found (panel A). The total L3 group is displayed in panel B. Because of the interaction between SMI, CRF and gender, separate analyses for men and women were performed in the L3 group. For women in the L3 group no association was found (panel C). For men in the L3 group an association was found (univariate linear analysis B 0.447, p 0.004; multivariate linear analysis B 0.345, p 0.039) (panel D).

in the L3 group. In women (n=62), higher SMI seemed to be associated with more CRF, but this was not statistically significant (B -0.401, 95% CI -0.867-0.065, p 0.090) (Table 3). No significant association between SMI and CRF was found in the T4 group (B 0.082, 95% CI -0.167-0.330, p 0.515). The association between SMI and CRF in the T4 group was modified by age ($B_{interaction}$ 0.024, 95% CI 0.005-0.043, p 0.014). SMI and CRF were not associated in any of the stratified analyses (several subgroups were defined: split at median age (61.9), and three groups age <50, 50-70, and >70).

DISCUSSION

Cancer related fatigue is a highly prevalent symptom that deteriorates quality of life. Both the current concepts of the multifactorial pathophysiology of CRF, and the efficacy of training interventions support the hypothesis that muscle wasting is associated with CRF. In the current study, 41% of the patients were diagnosed with CRF, and more than half of the patients in the L3

Table 3. Univariate and multivariate linear analysis

L3 - Total group	B	95%-CI lower bound	95%-CI upper bound	Sign.
Univariate	0.230	-0.004	0.464	0.054
Multivariate	0.142	-0.118	0.403	0.282
L3 - Men				
Univariate	0.447	0.143	0.751	0.004
Multivariate	0.345	0.017	0.672	0.039
L3 - Women				
Univariate	-0.422	-0.856	0.012	0.056
Multivariate	-0.401	-0.867	0.065	0.090
T4 - Total group				
Univariate	0.065	-0.139	0.269	0.530
Multivariate	0.082	-0.167	0.330	0.515

Univariate and multivariate analysis studying the association between Skeletal Muscle Index (SMI) and FACIT-fatigue scores. Multivariate analysis was performed with the following covariates: sex (L3-total group and T4 group); age; tumor type (L3 group); chemotherapy*; hormone therapy*; targeted therapy*; corticosteroid treatment (>10mg prednisolon/day for at least 3 weeks); first vs. ≥second line of chemotherapy; and Charlson Comorbidity Index (not age adjusted).
*as prior treatment in the past six months

group had a low SMI.[31] We found a significant association between higher muscle mass assessed at level L3 and lower fatigue levels in men, but not in women.

The significant association between muscle mass at level L3 and CRF in men is in line with a previous study by Kilgour et al.[20] who performed a cross-sectional study among 84 patients with inoperable (stage III-IV) gastro-intestinal or non-small cell lung cancer. Kilgour et al. have found a significant univariate negative correlation (B -4.8, p<.01) between fatigue measured with the Brief Fatigue Inventory and muscle mass measured with DXA (SMMI). In the multivariate analysis the association between muscle mass and fatigue was modified by gender. Subgroup analysis showed that fatigue scores had a strong negative correlation with muscle mass in men (r-0.60, p<0.001), but not in women. In the current study we were able to confirm these results in a larger group of patients with more diverse tumor types, while using other, also well-validated instruments to measure CRF and muscle mass. Kilgour et al. suggested that the different results for men and women were possibly related to absolute differences in muscle mass between men and women, or differences in BMI or circulating sex hormones. In the current study, the median muscle mass index for men in the L3 group is on the lower end of the SMMI-range in the study by Kilgour et al. when using the equation provided by Mourtzakis et al.[29], but still a relation with fatigue is found in these men. The lower SMI of women is therefore possibly not the only explanation for this result. BMI did also not differ between the men and women in the L3 group in the current study. No measurements of sex hormones were performed in the current study. Approximately half of the males in the L3 group were diagnosed with prostate cancer and were pretreated with androgen deprivation therapy, but the diagnosis prostate cancer was not a predictive factor for fatigue.

Muscle mass and fatigue for women in the L3 group were not only unrelated, but we even found a trend towards higher fatigue levels in women with higher muscle mass. Almost half of these women were diagnosed with breast cancer and frequently pretreated with hormone or chemotherapy, which may have resulted in a selection bias for women with less fatigue, or who have already participated in exercise programs during/after previous treatment lines.

An important strength of this study is the use of reliable, validated instruments to assess CRF[23,24] as well as the objective assessment of muscle mass[34] in a relatively large group of patients with advanced cancer. Although the assessment of muscle mass at L3 level is well validated,[35] muscle mass assessment at T4 level needs validation. No correlation between muscle mass and fatigue was present in the T4 group. Although this result might be influenced by a limited sample size in the gender specific subgroups or differences in tumor types, it could also be possible that the measurement of muscle mass at level T4 is less reliable.

A possible limitation from our study is the fact that most likely other factors influence fatigue in patients with advanced cancer. In the current study the effect of pain and distress, which can also influence fatigue scores,[1] was not evaluated. Furthermore, central aspects of CRF, such as the effect of serotonin and cortisol levels on the functioning of the suprachiasmatic nucleus, may play a major role in its severity, independent from their effect on muscle mass.[4] The positive effect of endurance exercise on CRF may be related to these central effects.[6] The study by Lovgren et al in lung cancer patients also suggests that women experience more problems with emotional functioning than men, which may also result in higher levels of fatigue.[36]

Second, we may have included a relatively fit group of patients with a good performance status and low comorbidity. Therefore, patients with an extremely low SMI or high fatigue levels may have been excluded on forehand because of a poor performance status. This bias should be taken into account when generalizing these results to other patient groups. From the current data could not be extrapolated whether this may have also been a factor contributing to the absence of a correlation between SMI and CRF in women.

Third, because this is a cross-sectional study causality cannot be assumed. Future studies need to confirm that an increase in muscle mass actually leads to a reduced fatigue level in men with advanced cancer. This may be of major clinical importance as fatigue is one of the most common symptoms in patient with advanced cancer, for whom quality of life is generally (one of) the most important factor(s) in treatment decisions. From our perspective, patients with progressively advanced cancer do often have benefit from effective palliative chemotherapy in the sense of improving their condition by reducing their tumor burden. Combining cancer treatment with exercise and/or dietary interventions that increase muscle mass may help to further improve treatment tolerance and results.

CONCLUSION

We found a significant association between muscle mass and CRF in men with advanced cancer, but not in women. These findings may lead to the suggestion that exercising may potentially be beneficial to reduce or prevent fatigue in men by increasing muscle mass. The absence of a relation

between SMI and CRF in women and the limited strength of the association in men highlight that CRF is a multifactorial problem. To further reduce CRF in both men and women with cancer, multifactorial assessments need to be performed in order to develop effective treatment strategies.

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9

PROPHYLACTIC TREATMENT FOR DELAYED CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING AFTER NON-AC BASED MODERATELY EMETOGENIC CHEMOTHERAPY: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

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ABSTRACT

Purpose

Delayed chemotherapy-induced nausea and vomiting (CINV) remains an important adverse effect of moderately emetogenic chemotherapy not containing anthracyclines and cyclophosphamide (non-AC MEC). We reviewed the current literature to update recommendations for delayed CINV prophylaxis after non-AC MEC.

Methods

A search of MEDLINE, and conference proceedings from the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO), and the Multinational Association for Supportive Care in Cancer (MASCC) was conducted from 2009 to July 31th 2014. Randomized controlled trials (RCTs) were identified comparing the efficacy of different antiemetic strategies. Trials with mixed AC and non-AC based regimens were also included.

Results

Upon literature search of 221 articles, 9 eligible RCTs were identified. Of the 9 included RCTs, there were a total of 18 study arms, and 2,110 patients randomized. RCTs reported outcomes on palonosetron, a dexamethasone-sparing regimen with palonosetron, netupitant, olanzapine, and megesterol acetate. There is insufficient data to decide whether palonosetron is the preferred 5-HT_3 receptor antagonist for delayed CINV prophylaxis after non-AC MEC. Single-day regimen of dexamethasone and palonosetron is non-inferior to palonosetron with multiday dexamethasone. The addition of an NK_1 receptor antagonist to first-generation 5-HT_3 receptor antagonists does not significantly improve the incidence of delayed CINV after non-AC MEC. NEPA, olanzapine, and megesterol acetate showed highly effective CR rates. Future RCTs are needed to assess these new antiemetics as a first-line prophylactic treatment for delayed CINV after non-AC MEC.

Conclusion

There is no high level evidence that will result in a change of recommendations for delayed CINV prophylaxis following non-AC MEC.

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV), particularly delayed CINV which occurs more than 24 hours after chemotherapy, remains an important and common adverse event complicating cancer treatment. Delayed CINV significantly interferes with patient's quality of life (QOL) and daily functioning.[1,2] Although the risk of delayed CINV has been studied best in regimens with high-dose cisplatin or combinations of anthracyclines plus cyclophosphamide (AC), also non-AC based moderately emetogenic chemotherapeutic regimens (non-AC MEC), causing emesis in 30-90% of patients, are associated with delayed CINV.[3-8]

In June 2009, MASCC and ESMO last updated their guidelines for the management of CINV in adults.[9] To prevent acute CINV induced by non-AC MEC, the guidelines recommend the use of a 5-HT_3 receptor antagonist combined with dexamethasone. The MASCC/ESMO guidelines do not support any particular 5-HT3 receptor antagonist over another. Multiday oral dexamethasone is recommended for delayed CINV prophylaxis following non-AC MMEC. ASCO published their last updated clinical practice guideline for antiemetics in oncology in 2011.[10] In this update, combined anthracycline and cyclophosphamide (AC) regimens were reclassified as highly emetogenic. For MEC regimens, the ASCO guideline recommends palonosetron in combination with multiday dexamethasone for the prevention of acute and delayed CINV. The phase III, double-blind, randomized trials upon which this recommendation is based, evaluated the combination of palonosetron and dexamethasone only in patients receiving HEC or AC chemotherapy, not MEC.[11,12] Moreover, it is unclear whether palonosetron would still be superior if aprepitant was used, as is recommended for HEC and AC in the international antiemetic guidelines.

Although the combination of palonosetron and multiday dexamethasone adequately controls acute CINV, a considerable amount of patients continues to experience delayed CINV. In a small observation trial in colorectal cancer patients with prophylactic palonosetron and single-dose dexamethasone, 15% of the patients did not achieve complete response (CR) or complete control (CC) in the delayed phase.[13] In another study, almost 25% of the patients treated with non-AC MEC did not achieve CR in the delayed phase, when palonosetron was combined with dexamethasone for 3 days.[14] In an unpublished observational study in patients treated with carboplatin-containing chemotherapy, delayed CINV remained a clinically significant problem despite administration of a 5-HT_3 receptor antagonist and dexamethasone: 22% of the patients reported moderate to severe delayed CINV, with symptoms persisting as long as 96 hours in 23% of the patients.[15] The need to establish new strategies for delayed CINV prophylaxis after non-AC MEC may therefore warrant more attention. The aim of this systematic review is to review the current literature to update recommendations for the prophylactic treatment of delayed CINV after non-AC MEC.

METHODS

An electronic search was undertaken of MEDLINE and conference proceedings of ASCO, ESMO, and MASCC from January 1th 2009 to July 31th 2014. Search terms included "chemotherapy-induced nausea and vomiting", "CINV", "emesis", "delayed nausea", "moderately emetogenic" and "MEC". The search was limited to articles published in English and in humans. Paediatric studies were

excluded. RCTs were included if they aimed to compare the efficacy of two or more antiemetic strategies in the prophylaxis of delayed CINV after the administration of moderately emetogenic chemotherapy not containing anthracyclines and cyclophosphamide (non-AC MEC) in at least one of the following five endpoints: CR, CC, no nausea, no vomiting, or no rescue medication. Studies including data on patients receiving HEC and/or AC, and non-AC MEC were included only if subgroup analysis of the non-AC MEC subgroup was performed. When data on AC and non-AC MEC were mixed in the subgroup analysis, we arbitrarily decided to include those studies in which the percentage of patients receiving AC was less than 50% in the subgroup. Both RCTs in which the antiemetic therapies only differed beyond day 1, and RCTs in which there was a difference starting at day 1 were included.

RESULTS

Results of the search strategy

Upon literature search of 221 articles, 9 eligible RCTs were identified (Figure 1).[14,16-23] Of the 9 included RCTs, there were a total of 18 study arms, and 2,110 patients randomized.

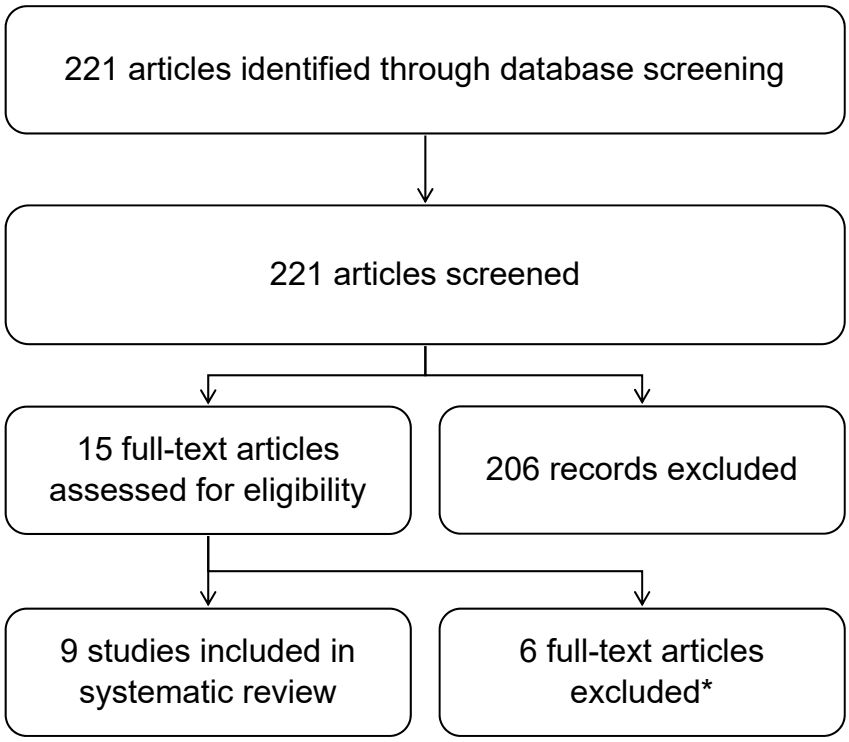
Characteristics of included RCTs

Clinical features of the included RCTs can be found in Table 1. Three RCTs included only patients receiving non-AC MEC,[16,19,20] whereas six RCTs included patients receiving chemotherapy with mixed emetogenicity: non-AC MEC and AC in two studies,[14,18] non-AC MEC and HEC in two studies,[21,23] and non-AC MEC, AC and HEC in another two studie.[17,22]

Two RCTs assessed the efficacy of palonosetron,[16,17] one assessed the non-inferiority of a dexamethasone-sparing regimen with palonosetron,[14] three the efficacy of NK1 receptor antagonists,[18-20] one the efficacy of NEPA,[21] one that of olanzapine,[22] and one assessed the efficacy of megestrol acetate.[23] Corticosteroids were administered to all but two studies.[17,23]

Palonosetron

An open-label, crossover trial was conducted in 30 patients with head and neck cancer, who received non-AC MEC (docetaxel 60 mg/m^2, carboplatin 300 mg/m^2, and 5-fluorouracil 600 mg/m^2).[16] In the first cycle, one group received palonosetron, the other ondansetron. Crossover of the antiemetic schedules was done for the subsequent cycle. It is unknown whether patients were chemotherapy-naïve or not in this study. Corticosteroids were administered to all patients on day 1. CR of vomiting during the acute, delayed, and overall phase was the primary outcome measure. CR in the acute phase was observed in 83.3% of the patients given palonosetron, and in 80% of the patients given ondansetron. In the delayed phase, CR was observed in 76.6% and 66.7% of the patients on palonosetron and ondansetron, respectively. The overall rate of CR was 66.7% in the palonosetron group and 46.7% in the ondansetron group. The authors did not provide P values. From this data, the authors concluded that palonosetron is clinically more efficacious than ondansetron in preventing acute and delayed CINV, although the difference is not statistically significant.



*4 articles were excluded because of lack of subgroup analysis for non-AC MEC, two were excluded because they were dose ranging studies

Figure 1. Study flow chart

In a multicenter, double-blind, non-inferiority, crossover trial, 144 patients with a broad range of tumor types received HEC (cisplatin), AC, or non-AC MEC.[17] One hundred and eight patients (75%) received AC or non-AC MEC. In this group, 68 patients (63%) received non-AC MEC (carboplatin and oxaliplatin-based regimens). Chemotherapy naïve and non-naïve patients were included. Corticosteroids were not allowed. The primary efficacy endpoint was the proportion of patients with CR (no vomiting) during the acute, delayed and overall phase. Because no carry over effect was observed with regard to the primary endpoint, the data of both cycles were pooled. In the overall population, the difference in CR rates between palonosetron and ondansetron was not statistically different: in the acute phase (71.09% vs. 65.22%, respectively, P = 0.28), in the delayed phase (60.16% vs. 55.80%, respectively, P = 0.46%), and in the overall phase (53.13% vs. 50.00%, P = 0.61). In the mixed AC and non-AC MEC subgroup analysis, the difference in CR rates between palonosetron and ondansetron was also not statistically different; in the acute phase (72.16% vs. 67.65%, respectively) in the delayed phase (67.01% vs. 59.80%, respectively), and in the overall phase (58.76% vs. 52.9%, respectively). P values were not provided for this subgroup analysis. The authors

Table 1. Characteristics of randomized controlled trials

Trial	Study design	Intervention	Chemotherapy emetogenicity	Efficacy sample size non-AC MEC subgroup	Role of adjuvant corticosteroids
Palonosetron					
Kaushal et al. (16)	Open-label, crossover	1) Palonosetron 0.25 mg 2) Ondansetron 16 mg	Non-AC MEC	1) 30 2) 30	Corticosteroids administered to all patients on day 1
Tian et al. (17)	Double-blind, non-inferiority, crossover	1) Palonosetron 0.25 mg 2) Granisetron 3 mg	HEC, AC, non-AC MEC	1) 54[a] 2) 54[a]	Corticosteroids not allowed
Dexamethasone-sparing regimens					
Celio et al. (14)	Open-label, non-inferiority, parallel	1) Palonosetron 0.25 mg + dexamethasone day 1 2) Palonosetron 0.25 mg + dexamethasone day 1-3	AC and non-AC MEC	1) 112 2) 103	Corticosteroids administered to all patients
NK_1 receptor antagonists					
Rapoport et al (18)	Double-blind, parallel,	1) Aprepitant + ondansetron 16 mg day 1 2) Placebo + ondansetron 16 mg day 1-3	AC and non-AC MEC	1) 230 2) 214	Corticosteroids administered to all patients on day 1
Hesketh et al. (19)	Double-blind, parallel	1) Casopitant 90 mg 2) Placebo	non-AC MEC	1) 355 2) 352	Corticosteroids administered to all patients on day 1

Table 1. (continued)

Trial	Study design	Intervention	Chemotherapy emetogenicity	Efficacy sample size non-AC MEC subgroup	Role of adjuvant corticosteroids
Tanioka et al. (20)	Double-blind, parallel, phase II	1) Aprepitant 2) Placebo	Non-AC MEC	1) 45 2) 46	Corticosteroids administered to all patients on day 1-3
NEPA					
Gralla et al. (21)	Double-blind, parallel	1) NEPA (Netupitant 300 mg / palonosetron 0.50 mg) 2) Aprepitant + palonosetron 0.50 mg	HEC, non-AC MEC	1) 233 2) 79	Corticosteroids administered to all patients on day 1 (MEC) or day 1-4 (HEC)
Olanzapine					
Tan et al. (22)	Open-label, parallel	1) Olanzapine 10 mg day 1-5 + dexamethasone day 1 2) Dexamethasone day 1-5	HEC, AC, non-AC MEC	1) 65[b] 2) 64[b]	Corticosteroids administered to all patients:
Megestrol acetate					
Zang et al. (23)	Single-blind, crossover	1) Megestrol acetate 160 mg day 1-4 2) Placebo day 1-4	HEC, non-AC MEC	1) 22 2) 22	Corticosteroids not allowed

AC: anthracycline / cyclophosphamide combination; non-AC MEC: moderately emetogenic chemotherapy not containing anthracyclines and cyclophosphamide; HEC: Highly emetogenic chemotherapy

a. combined AC and non-AC (non-AC: 63%)

b. combined AC and non-AC (non-AC: 55%)

concluded that palonosetron is not inferior to granisetron in preventing vomiting during all phases following HEC or AC / non-AC MEC.

Dexamethasone-reducing study

A multicenter, open-label, non-inferiority study published in 2011 was designed to evaluate the efficacy of palonosetron plus single-day dexamethasone compared with multiday dexamethasone. This study included 332 patients receiving AC or non-AC MEC, mainly oxaliplatin-, irinotecan-, and carboplatin-based regimens.[14] All patients were chemotherapy-naïve. The patients were randomized to receive palonosetron in combination with dexamethasone as either a single-dose or for 3 days to compare the efficacy in preventing acute and delayed CINV. Complete response (CR; defined as no vomiting and no rescue medication) during the overall phase (day 1-5) was the primary outcome measure. Subgroup analyses of each treatment group by type of chemotherapy (AC vs. non-AC) were done for CR during the acute and delayed phase. In the overall population, CR rates during the overall phase were 67.5% for single-dose dexamethasone, and 71.1% for those administered dexamethasone on day 1-3 (difference, 95% CI: -3.6% (-13.5 to 6.3)). In the subgroup analysis for non-AC-based chemotherapy, CR in the acute phase was 88.3% for single-dose dexamethasone vs. 87.0% for 3-day dexamethasone (difference, 95% CI: 1.3 (-7.6 to 10.2)). CR in the delayed phase was 71.2% for single-dose vs. 76.0% for 3-day dexamethasone (difference, 95% CI: -4.8 (-16.7 to 7)). The authors concluded that palonosetron plus single-dose dexamethasone administered before AC and non-AC-MEC regimens provides protection against acute and delayed CINV, which is non-inferior to that of palonosetron plus dexamethasone for 3 days.

NK_1 receptor antagonists

In a multicenter, double-blind trial, 848 patients receiving AC and non-AC MEC regimens for a broad range of tumors, were randomized to compare the efficacy of on oral three-drug regimen of aprepitant, ondansetron and dexamethasone to an oral control regimen of ondansetron and dexamethasone.[18] Fifty-two percent of the patients were given non-AC-based MEC, including oxaliplatin, carboplatin, ifosfamide, and irinotecan. All patients were chemotherapy-naïve. The primary efficacy endpoint of the study was the proportion of patients reporting no vomiting during the overall phase. Subgroup analysis of the non-AC MEC treated patients for vomiting during the acute and delayed phase was post hoc. In the overall population, a significantly higher proportion of patients on aprepitant reported no vomiting compared to the control group in the overall phase (76.2% versus 62.1%, $P < 0.001$). Among those receiving non-AC-based chemotherapy regimens, more patients in the aprepitant group reported no vomiting compared to the control group in all phases (overall: 83.2% vs. 71.3%, $P < 0.05$; acute: 96.5% vs. 91.6%, $P < 0.05$; delayed 84.5% vs. 73.9%, $P < 0.05$). The authors concluded that the three-drug regimen of aprepitant, ondansetron, and dexamethasone results in a significantly improved prevention of CINV for patients receiving AC and non-AC-based MEC.

In a double-blind parallel group study, which enrolled 707 patients receiving non-AC MEC (oxaliplatin) for colorectal cancer, the efficacy of single-dose casopitant was compared to placebo, added to ondansetron on days 1-3 plus dexamethasone on day 1.[19] All patients were chemotherapy-

naïve. The primary endpoint in this study was the percentage of patients achieving CR (no vomiting, no use of rescue medication) during the overall phase. In the casopitant group, 86% of patients vs. 85% in the placebo group achieved CR (P = 0.7273). Results were similar for CR rates in the acute phase (97% vs. 96%, respectively, P = 0.4771) and delayed phase (86% vs. 85%, respectively, P = 0.7273). No difference in severity of nausea was observed between treatment groups in either the acute or delayed phase. The authors concluded that the addition of single-dose casopitant to a regimen consisting of ondansetron and dexamethasone does not improve the control of CINV in any phase after oxaliplatin-based non-AC MEC.

Ninety-one female patients younger than 70 years, treated with non-AC MEC regimens (carboplatin or irinotecan-based), were randomized to aprepitant or placebo in a multicenter, double-blind, phase II trial.[20] Most tumors were of gynaecological origin. All patients received granisetron and multi-day corticosteroids. It is unknown whether patients were chemotherapy-naïve or not in this study. The primary endpoint was CR (no vomiting, no rescue medication) during the overall phase of the first cycle. The CR rate in the overall phase was superior but not significantly higher in the aprepitant group than in the placebo group (62% vs. 52%, respectively, P = 0.33). There was also no significant difference in CR rate for the acute and delayed phases: (98% vs. 96%, respectively, and 62% vs. 52%, respectively). The authors concluded that the aprepitant regimen provides superior efficacy in the treatment of CINV after non-AC MEC, although the difference is not statistically different.

NEPA, a fixed-dose combination of netupitant and palonosetron

In a multicenter, double-blind trial, the efficacy of a single dose of NEPA (oral fixed-dose combination of 300 mg netupitant and 0.50 mg palonosetron) was compared to oral aprepitant plus oral palonosetron 0.50 mg in 413 patients treated with either HEC or non-AC MEC regimens for a broad range of tumors.[21] Seventy-six percent of the patients received non-AC MEC, mainly carboplatin and oxaliplatin-based. In this study, the dose/schedule of oral dexamethasone was open-label and based on the emetogenicity of the chemotherapeutic regimen. All patients were chemotherapy-naïve. The study was designed primarily to assess the safety of NEPA, but also assessed the efficacy of this antiemetic drug. The overall incidence, type and frequency of adverse events were comparable between the treatment groups. In the overall population, CR rates (no vomiting, no use of rescue medication) in the overall phase were similar in cycle 1 (81% in the NEPA group vs. 76% in the control arm). The reported control of nausea was high in both groups and not statistically different: 84%-92% across cycles for NEPA, and 81%-87% for the control group. For the non-AC MEC subgroup, CR rates across cycles were also comparable between the treatment groups: 80%-93% in the NEPA group, and 82%-89% in the control group. The authors concluded that NEPA is well tolerated and highly effective over multiple cycles of HEC or non-AC MEC.

Olanzapine

In 229 patients with a broad range of tumors, the efficacy of olanzapine was compared to the 5-HT_3 receptor antagonist azasetron in an open-label trial.[22] Patients received HEC, AC, or non-AC MEC, and were randomized to olanzapine 10 mg days 1-5 plus azasetron 10 mg iv. and dexamethasone 10

mg iv. on day 1, or to the control group with azasetron 10 mg iv. on day 1 plus dexamethasone 10 mg iv. days 1-5. Both chemotherapy-naïve and non-naïve patients were included. Fifty-six percent of all randomized patients received AC or non-AC MEC. In this combined subgroup, 55% of the patients received non-AC MEC, mainly oxaliplatin-based regimens. The primary endpoint was CR (no nausea and vomiting, no use of rescue medication) for the acute, delayed and overall phase. In the overall population, CR rates for acute nausea and vomiting were very high in all groups (>95%), and not statistically different for both HEC and the combined AC and non-AC MEC subgroup. In the combined AC and non-AC MEC subgroup, CR rates for delayed nausea and vomiting were 83% for the olanzapine group vs. 58% for the control group ($P < 0.05$). CR rates for the overall phase in this subgroup were 83% and 56%, respectively ($P < 0.05$). The authors concluded that olanzapine significantly improves the CR of CINV in the acute, delayed, and overall phase for patients receiving both HEC and AC or non-AC MEC.

Megestrol acetate

One hundred patients with gastrointestinal tumors or lung cancer, and treated with HEC or non-AC MEC (mainly oxaliplatin and irinotecan-based regimens) were randomized in a single-blind, crossover trial to receive either oral megestrol acetate 320 mg or placebo.[23] Corticosteroids were not all allowed in this study. Information on previous treatment with chemotherapy was not provided. Rates of complete protection against vomiting and moderate-to-severe nausea were primary endpoints. In the non-AC MEC subgroup (44% of all included patients), complete protection rates for megestrol acetate compared to the control group were 50% vs. 27.3% in the overall phase ($P = 0.002$), 72.7% vs. 59.1% in the acute phase ($P = 0.146$), and 52.3% and 25.0% in the delayed phase ($P = 0.000$), respectively. The authors concluded that megestrol acetate is highly effective to prevent CINV in all phases for both HEC and non-AC MEC.

DISCUSSION

This systematic review of RCTs provides an update of clinical evidence on recommendations for the prevention of delayed CINV after non-AC MEC. We identified two trials comparing the efficacy of palonosetron to first-generation 5-HT_3 receptor antagonists. The study by Kaushal *et al*. reported a clinically but not significantly benefit of palonosetron compared to ondansetron.[16] The study population in this trial was small however, 30 patients only. Another limitation is, that it has an open-label, crossover design. The second study by Tian *et al*. concluded that palonosetron is not inferior to granisetron in preventing vomiting during all phases after MEC.[17] This conclusion is based on a subgroup analysis of only 108 patients, in which AC and non-AC MEC (63%) were combined. Also, corticosteroids were not allowed in this study, which is in contrast with recommendations from international antiemetic guidelines. Altogether, these studies suggest that palonosetron is equally effective as first-generation 5HT_3 receptor antagonists for the prevention of delayed CINV after non-AC MEC. Recently, Roscoe *et al*. also found in a large trial in patients receiving HEC, AC, and non-AC MEC, that palonosetron was not more effective than granisetron in rate of average delayed nausea (primary endpoint), when both were combined with dexamethasone

and prochlorperazine.[24] We did not include this RCT in our review, because Roscoe *et al.* did not perform a subgroup analysis for non-AC MEC regimens. These conclusions are contrary to results from a recently performed systematic review and meta-analysis by Popovic *et al.*, which compared the efficacy and safety of palonosetron to other 5-HT_3 receptor antagonists in CINV prophylaxis.[25] In this review, which also included the RCTs we identified, it was shown that palonosetron is statistically superior to other 5-HT_3 receptor antagonists for the prevention of delayed CINV in the endpoints of CR (OR = 1.90, 95% CI 1.47-2.45) and CC (OR = 1.87, 95% CI 1.45-2.41). It is worth mentioning that this meta-analysis did not specifically address the efficacy of palonosetron for delayed CINV prophylaxis following non-AC MEC, because data from AC and non-AC MEC were pooled. Considering this, we conclude that at present there is still insufficient data to decide whether palonosetron is the preferred 5-HT_3 receptor antagonist for delayed CINV prophylaxis after non-AC MEC.

Current antiemetic guidelines, in addition to the use of 5-HT_3 receptor antagonists, recommend the use of multiday dexamethasone to prevent acute and delayed CINV after non-AC MEC. However, dexamethasone is often accompanied by unpleasant side effects. Reduction of dexamethasone exposure, without a decrease in efficacy, could be beneficial for patients. One clinical trial reported that the efficacy of a single-day regimen of palonosetron and dexamethasone is non-inferior to multiday dexamethasone.[14] Subgroup analysis of non-AC based regimens was performed. The percentage of patients with no vomiting was not significantly different between the two treatment groups in the acute, delayed, and overall phases following non-AC MEC. This evidence may be of particular benefit to patients undergoing multiple cycles of therapy when palonosetron is prescribed, and where the long-term side effects of dexamethasone can be reduced.

While the major guidelines do not recommend the use of an NK_1 receptor antagonist for non-AC MEC, there is some evidence that adding aprepitant may improve control of vomiting. Rapoport *et al.* found that a significantly higher proportion of patients on aprepitant reported the primary outcome of no vomiting during the overall phase. Results are consistent in the non-AC subgroup during all phases.[18] The subgroup analysis for MEC regimens however, was not predefined. Also, ondansetron was used as an active control arm for delayed CINV prophylaxis, which is not justified by clinical evidence.[26] The results of this study are in contrast with data from the study that was performed by Hesketh *et al.*[19] They found no additional effect of casopitant to ondansetron and dexamethasone in patients treated with MEC. Again, ondansetron was used as an active control arm, which is not recommended by the guidelines. Tanioka *et al.* failed to prove an additional effect of a NK_1 receptor antagonist either.[20] All patients received granisetron and multiday corticosteroids in this study, therefore presenting an adequately efficacious control arm. Although the authors suggest that adding aprepitant improves CINV prophylaxis, CR rates were not significantly different. Taken together, the results of these studies suggest that the addition of a NK_1 receptor antagonist to first-generation 5-HT_3 receptor antagonists does not significantly improve the incidence of delayed CINV after non-AC MEC, when compared to an appropriate control arm.

Several studies suggest that a three-drug combination of an NK_1 receptor antagonist, palonosetron, and dexamethasone causes high CR rates in patients undergoing HEC or non-AC

MEC.[27,28] This led to the drug development of NEPA, which is an oral fixed-dose combination of netupitant, a highly selective NK_1 receptor antagonist, and palonosetron. We found one study, which concluded that this drug was safe, well tolerated, and highly effective in patients treated with , when compared to oral 3-day aprepitant and palonosetron, and when both treatment groups are combined with dexamethasone.[21] Although this antiemetic drug is promising, future RCTs should be performed to investigate the efficacy of NEPA in clearly predefined MEC groups, when compared to a standard antiemetic regimen.

New anti-CINV regimens for non-AC MEC are evolving. Recently, it was noticed that olanzapine, an atypical antipsychotic, combined with a single dose of dexamethasone and palonosetron was very effective at controlling acute and delayed CINV in patients receiving HEC.[29] Tan *et al*. found highly significant CR rates for delayed CINV prophylaxis following non-AC MEC, with multiday olanzapine compared to multiday dexamethasone.[22] However, this study had an open-label design, which could have influenced the results. Moreover, AC regimens (27% of all patients) were included in the MEC subgroup analysis. Therefore, at present there is insufficient evidence to recommend olanzapine for delayed CINV prophylaxis after MEC regimens. Future studies in clearly defined MEC populations should assess whether the use of olanzapine results in better CR rates for delayed CINV after non-AC MEC.

The antiemetic potential of megestrol acetate was assessed in one trial in a small group of patients, receiving chemotherapy with mixed emetogenicity.[23] The authors reported highly significant CR rates for non-AC MEC treated patients, when megestrol acetate was compared to placebo. All patients received granisetron and metoclopramide, but corticosteroids were not allowed. Subgroup analysis for MEC contained both AC and non-AC regimens. Again, future RCTs should assess the efficacy of megestrol acetate in clearly predefined MEC groups, when compared to a control arm containing standard antiemetics.

There are certain limitations of this review. First, data of the included RCTs could not be synthesized because of the heterogeneity of antiemetic regimens used in the included studies. Additionally, a limitation of all included RCTs is the variance in primary outcomes, which makes comparisons complicated. Also, differences between arms for the acute phase may have a carry-over effect on delayed phase results. Finally, most subgroup analyses were performed in populations receiving chemotherapy with mixed emetogenicity, making it hard to draw firm conclusions for non-AC MEC regimens.

We conclude that high level evidence for optimal prophylaxis of delayed CINV after non-AC MEC is lacking. Therefore, many important issues remain unanswered. Future RCTs in clearly defined non-AC MEC treated patients should discuss the merits of including palonosetron or regimens containing new antiemetics, like olanzapine, as a first-line prophylactic treatment for delayed CINV.

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10

SUMMARIZING DISCUSSION AND FUTURE PERSPECTIVES

SUMMARIZING DISCUSSION AND FUTURE PERSPECTIVES

Patients diagnosed with advanced cancer face a trialing time knowing they will have to face symptoms caused by their disease, possible side effects of treatment, and finally death. Palliative care is provided to these patients with attention to psychological and social challenges as well as physical symptoms, in order to improve their quality of life. Although advances have been made, there is a lack of literature on evidence based treatment of symptoms that patients with advanced cancer may experience. In this thesis several symptoms that are common in this phase and have a major impact on quality of life were studied.

DELIRIUM

Delirium is one of the most common neuropsychiatric complications seen in patients with advanced cancer, especially during hospitalization.[1,2] It is associated with increased morbidity, mortality, and interference with symptom assessment and control.[3-5] It impedes the communication of patients with their families, and hinders patient participation in treatment decision making. Therefore, effective detection and treatment of delirium is of utmost importance in the care of hospitalized patients with cancer.

In chapter 2, the prevalence of delirium in a hospitalized population in patients with cancer was studied. Compared to previous literature,[6,7] we found a low prevalence of delirium of approximately 3 percent in this population. The main reasons for this low prevalence are good clinical care with early treatment of precipitating factors; delirium prevention methods which were already implemented on the hospital ward comparable to the HELP program;[8] and the chance that delirium episodes were missed despite our efforts, as discussed in chapter 2. With the large number of patients in this study, we were able to build a prediction model that identifies patients with a negligible risk of delirium, and patients at high risk of developing delirium. For the first group, a possible recommendation is not to invest in screening efforts as they may be costly, time-consuming and/or bothersome for the patient. For the high risk group, measures should be taken to prevent the development of delirium for patients admitted to the hospital without delirium. Furthermore, it is of utmost importance to detect delirium as early as possible, and to prescribe effective treatment, as for most patients and their relatives delirium is a traumatizing experience.[3]

To optimize screening for delirium, we tested the accuracy of the Delirium Observational Screening scale, a nurse-rated observational instrument. Chapter 3 showed that this instrument is very accurate in detecting delirium.

Once a patient is diagnosed with delirium, action should be taken to treat the underlying cause(s) when possible. In the meantime symptomatic treatment should be considered, especially when it is hard to identify the underlying cause, or when treatment of this underlying cause is not possible. In chapter 4 we compared the efficacy and side effects of olanzapine to haloperidol. This study showed no statistically significant benefit of olanzapine compared to haloperidol. The side effect profile of olanzapine seemed to be better than that of haloperidol, but we did not have enough statistical power to draw firm conclusions for this endpoint. A limitation to this study was the fact that we did not use a placebo control group. During the designing phase of this study

the general consensus was that delirium was a palliative emergency that could not be left without drug treatment, but a recent study by Agar et al suggested that antipsychotic medication was not more effective than placebo.[9] Several comments have been raised with respect to this study, among which the low doses of antipsychotic medication used (max 1-2mg haloperidol depending on the patient's age), where one can question whether effective doses have been tested.[10] An important principle of evidence based medicine is that a drug prescribed to patients should be proven to be better than placebo. Therefore we advocate future studies on delirium treatment to include a placebo group.

An important observation during this study was that, although many patients did not respond to the assigned treatment, and others may have also recovered without treatment, there were some patients who were evident rapid responders while the presumed underlying cause(s) could not be treated. Therefore, we support the suggestion by Bogman et al not to abandon current practice to prescribe antipsychotics to patient with delirium while awaiting placebo-controlled trials.[10] Future studies should explore the pathophysiology of delirium, where it may be very well possible that different delirium subtypes have different causes, and find ways to predict treatment response.

Further study is needed on effective prevention of delirium in the hospital for patients who are not delirious upon admission. Many studies have focused on adjustments in the health care environment,[8,11,12] of which only the HELP program has shown statistically significant clinical benefit.[8] In chapter 2 we identified patients at high risk of developing delirium. After external validation, it could be of interest to study prophylactic drug treatment in these patients. However, studies with various antipsychotics, benzodiazepines and other drugs in patients admitted to the intensive care unit or scheduled surgical interventions have been unsuccessful thus far.[13,14] Therefore, careful selection of the drug of choice and patients who are at risk is of utmost importance. Furthermore, pilot studies and early stopping rules should be implicated in these study types to prevent patients from possibly harmful treatment.

OPIOID INDUCED CONSTIPATION

Many patients with cancer will need opioids at some point during their disease trajectory.[15] Opioid-induced constipation (OIC) is a frequently described side effect of opioid treatment and can have a major impact on a patient's quality of life.[15,16] Although there are some data on the prevalence of OIC in the registration studies of several opioid subtypes, little is known on its prevalence in daily oncology practice, especially for the most recently introduced synthetic opioid subtypes. Even less is known about the efficacy of prophylactic laxative treatment, or which treatment is most effective if a patient has developed OIC. Guidelines on this subject are mostly extrapolated from studies on the treatment of chronic constipation in otherwise healthy subjects, with the addition of mu-opioid receptor antagonists if other treatments fail.

In chapter 5 and 6 we studied the prevalence of opioid induced constipation in daily oncology practice. We showed that twelve percent of the patients on opioids suffer from constipation. In chapter 5 we present the study protocol of a trial looking into the effects of the mu-receptor

antagonist methylnaltrexone. This trial focused on the effect of this drug in patients using different opioid subtypes (morphine, fentanyl and oxycodone). Including patients in this observational trial proved to be very difficult, mainly because many patients used a combination of different opioid subtypes. Furthermore patients refused treatment with methylnaltrexone because they were not keen on getting injections and feared the possible side effects of this drug. Therefore, the results of this trial could only be representing a very small proportion of the patients using opioids, and would have minimal impact on daily practice. This led to the decision to terminate this trial. Recent publications show effective treatment of opioid induced constipation by the oral μ-receptor antagonist naldemedine.[16-20] In this studies the effect percentage is about 70 percent in patients with cancer with OIC, without signs of naldemedine-induced opioid withdrawal. The opioid subtypes used by these patients were however not reported.

The second objective of this trial was to study the immunomodulatory and anti-angiogenic effects of methylnaltrexone. Unfortunately, the few patients who were included in the trial did not meet the inclusion criteria for this part of the study, or refused the extra blood withdrawal which was needed. Therefore, we were not able to show results on this part of the study. Recent publications on this subject showed that naloxone and methylnaltrexone may have a beneficiary effect on disease progression and survival in cancer patients.[21,22] Therefore it could be argued to start an exploratory trial in patients with cancer to study the potential of methylnaltrexone or the oral u-receptor antagonist naldemedine as anti-cancer treatment.

CANCER RELATED FATIGUE

Cancer related fatigue can be a result of both the cancer itself and the treatments given to the patient. It is one of the best known symptoms of cancer, sometimes present months before diagnosis.[23] Chapter 7 provides an overview of what was known thus far on the pathophysiology of CRF and possible treatment options. Since writing this review, several articles on this subject have been published, mostly reviews showing the efficacy of exercise.[24-26] New studies on pharmacological treatment of CRF show negative results for treatment of patients with CRF with modafinil and armodafil,[27-30] and mixed results for methylphenidate in two small studies,[31,32] and no effect in a placebo-controlled study where patients were their own control.[33] Two small studies on methylprednisolone in a palliative care setting possibly confirm the suggestion that corticosteroids might be effective for patients with CRF with limited life-expectancy.[34,35] Ashrafi *et al* report positive results for bupropion in a small placebo-controlled study, but this is mostly based on a difference in baseline fatigue levels between the two groups.[36] Hoenemeyer *et al*, and Zhou *et al* have recently published a study on open-label placebo treatment for patients with CRF, showing remarkable positive results.[37,38] This highlights the importance of placebo-controlled studies on this subject. With the pathophysiological mechanisms described in chapter 7 and the effect of corticosteroids in mind, it might be of interest to study the effect of NSAIDs on CRF. Although these drugs also have limitations in their use in patients with renal insufficiency or who are treated with chemotherapy that might cause renal failure.

In chapter 8 we studied the correlation between muscle mass and cancer related fatigue in patients starting palliative chemotherapy for solid tumors. Results of this study showed a modest correlation. Since the pathophysiology of cancer related fatigue is still nog clear and probably multifactorial it is hard to pinpoint whether both CRF and muscle mass are affected by the same process, or that loss of muscle mass is on the pathway to develop CRF, or that both mechanisms are present. The findings of this study do support the fact that exercise is one of the few interventions that has shown some efficacy on CRF.[24-26] Future studies may incorporate exercise with dietary advice and psychological support.

CHEMOTHERAPY INDUCED NAUSEA AND VOMITING

In chapter 9 we reviewed the efficacy of anti-emetic treatment on nausea and vomiting after moderately emetogenic chemotherapy. In this systematic review we showed that there is a knowledge gap on this subject, as most drugs were tested in patients receiving highly emetic chemotherapy. Therefore, the MEDEA study was started. In this study the efficacy of the combination of palonosetron and dexamethasone was compared to ondansetron and dexamethasone, and to the combination of ondansetron, dexamethason and metoclopramide in patients receiving moderately emetogenic non-AC-based chemotherapy. Results of this study are expected soon.

FUTURE PERSPECTIVES

Delirium has a major impact on the quality of life, especially in the dying phase where it hampers communication with the people who are close to the patient. Prevention, early detection and optimal treatment of delirium should have high priority in daily oncology practice. In this thesis the development of a prediction model for delirium in patients with advanced cancer was described. External validation of this model is necessary to develop a model that can be used in the clinic to guide cost-effective delirium screening and preventative measures. Department wide implementation of non-medical preventative measures for delirium, as described in the HELP program for example,[8] can help to reduce the incidence of delirium. Future studies should focus on clarifying the pathophysiology of delirium with specific attention for the different delirium subtypes. Furthermore, placebo-controlled trials are needed for the treatment of delirium.

Future studies on opioid induced constipation should first of all aim to define the best prophylactic treatment, and then to identify the best treatment protocol for in case a patient develops OIC despite prophylactic treatment. Naldemedine, a selective mu-receptor antagonist which can be used orally, may have a prominent role in these studies. Furthermore, the effect of opioids and mu-receptor antagonists on tumor progression should be studied.

For cancer related fatigue, which seems to be a multifactorial problem, a multi-component intervention should be developed. This should include psychological support, nutritional advice, exercise and possibly a drug intervention. If drugs are studied for their effect on fatigue a placebo control is of utmost importance, with regards to the recent studies of Hoenemeyer et al and Zhou et al.[37,38]

In the last years several anti-emetics have been developed, mostly aimed at the patients with the highest need; those treated with highly-emetogenic chemotherapy. The effects of these anti-emetics in moderately emetogenic chemotherapy have received less attention and should be further studied. Especially how these new, and often more expensive, drugs compare to older less expensive treatment regiments. The MEDEA study is a good step in this direction and may hopefully give some guidance on this subject.

IN CONCLUSION

Patients with advanced cancer are at risk for a multitude of symptoms affecting their quality of life. In this thesis several of these are addressed. Most of these symptoms have a multifactorial pathophysiology, which makes studies on their origin and possible treatment options difficult. Combined effort of the scientific community helps to unravel these complicated subjects and make patient tailored treatment possible. Patients with advanced cancer are a vulnerable group, but when possible personal benefit and the risk at side effects are balanced, it is possible to perform trials with these patients.

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11

NEDERLANDSE WETENSCHAPPELIJKE SAMENVATTING

NEDERLANDSE WETENSCHAPPELIJKE SAMENVATTING

Elk jaar krijgen meer dan 100.000 Nederlanders te horen dat ze kanker hebben.[1] Screeningsprogramma's waardoor kanker in een vroeg stadium ontdekt wordt en nieuwe behandelingen zorgen er voor dat de overleving verbetert. Desondanks sterven circa 45.000 mensen per jaar aan de gevolgen van kanker.[2] In de tijd tussen het vaststellen van een ongeneeslijke ziekte en het daadwerkelijke overlijden wordt palliatieve zorg verleend. Hierbij wordt een balans gezocht tussen eventuele behandelingen die het leven zouden kunnen verlengen en de kwaliteit van leven in deze periode. Een belangrijk onderdeel van de zorg in deze tijd is het bestrijden van symptomen van de ziekte en bijwerkingen van de behandeling. In dit proefschrift wordt onderzoek beschreven naar een aantal veel voorkomende symptomen met grote invloed op de kwaliteit van leven.

DELIER

Het delier is een van de meest voorkomende neuropsychiatrische aandoeningen in patiënten met een gevorderd stadium van kanker.[3,4] Het kan kort omschreven worden als acuut ontstane verwardheid die het gevolg is van een lichamelijke aandoening (bijvoorbeeld een blaasontsteking). Het treedt dan ook vaak op tijdens een opname in het ziekenhuis en belemmert dan effectieve communicatie met de patiënt over zijn/haar wensen in het zorgverleningsproces. Daarnaast kan het moeizame contact met de familie tijdens een delier een grote invloed hebben op de beleving van het moment van overlijden.[5-7] Het is dan ook van groot belang een delier indien mogelijk te voorkomen, maar als het op treedt tijdig te herkennen en adequaat te behandelen.

In hoofdstuk 2 worden de kenmerken van patiënten die opgenomen worden op de oncologie afdeling van een universitair medisch centrum bestudeerd in de relatie tot het ontwikkelen van een delier. De kenmerken die het sterkste onderscheid maakten tussen patiënten die wel of geen delier ontwikkelden zijn gebruikt om een voorspellend model te bouwen voor het ontwikkelen van een delier bij opname in het ziekenhuis. Voor de patiënten die een laag risico hebben op het ontwikkelen van een delier lijkt het niet nodig om extra te investeren in maatregelen om de kans op delier verder te reduceren of om extra in te zetten op vroege detectie. Bij patiënten met een hoog risico op het ontwikkelen van een delier lijkt dit wel de moeite waard. Na externe validatie van het voorspellende model dat hier ontwikkeld is, zou dit ingezet kunnen worden om patiënten te selecteren voor intensievere screeningsprogramma's of (onderzoek naar) preventieve behandeling.

In hoofdstuk 3 wordt aangetoond dat de DOS-vragenlijst (Delier Observatie en Screening) betrouwbaar te gebruiken is bij patiënten met kanker die opgenomen zijn in het ziekenhuis. Een groot voordeel van de DOS is dat deze door verpleegkundigen afgenomen wordt; zij hebben vaak intensief contact met de patiënt en kunnen veranderingen in gedrag hierdoor snel herkennen.

Screening op delier heeft echter alleen zin wanneer het stellen van de diagnose ook behandelconsequenties heeft. Naast onderzoek naar de onderliggende oorzaak van het delier en zo mogelijk behandeling hiervan, lijkt er een plaats voor medicamenteuze behandeling.[8,9] Met name voor patiënten waarbij de onderliggende oorzaak niet eenvoudig weg te nemen is, kan

verlichting van de symptomen van groot belang zijn. In de huidige richtlijnen is haldol het middel van eerste keus.[8,9] Haldol is echter slechts bij circa 50% van de patiënten effectief en bijwerkingen zoals slaperigheid en rigiditeit beperken het gebruik.[10] In hoofdstuk 4 wordt gekeken naar de effectiviteit van olanzapine in vergelijking met haldol in een gerandomiseerde studie. Helaas bleek dit laatste middel niet effectiever dan haldol. Voor het beoordelen van de bijwerkingen heeft deze studie niet voldoende power. Verder onderzoek om de preventie en behandeling van een delier te optimaliseren blijft dus noodzakelijk.

OBSTIPATIE DOOR OPIOÏDGEBRUIK

Een groot deel van de patiënten met kanker hebben ergens in hun ziektetraject opioïden nodig voor adequate pijnstilling.[11] Obstipatie is een veelgenoemde bijwerking van opioïden die veel invloed kan hebben op de kwaliteit van leven.[11,12] Er is echter weinig bekend over het daadwerkelijke voorkomen hiervan in de dagelijkse praktijk in de zorg voor patiënten met kanker. In hoofdstuk 5 en 6 wordt de prevalentie van opioïd-geïnduceerde obstipatie bestudeerd en welke laxantia preventief en/of als behandeling hiervan gebruikt worden. Dit onderzoek laat zien dat circa twaalf procent van de patiënten die opioïden gebruiken last heeft van obstipatie, ondanks het voorschrijven van profylactische laxantia. In een prospectieve studie wordt specifiek gekeken naar de effectiviteit van methylnaltrexon, een mu-opioïdreceptorantagonist, bij patiënten die verschillende subtypes opioïden gebruiken. Doordat patiënten vaak een combinatie van verschillende subtypes opioïden gebruikten, kwamen er weinig in aanmerking voor deze studie. Tevens waren er patiënten die afzagen van het gebruik van methylnaltrexon vanwege weerstand tegen het krijgen van subcutane injecties of angst voor bijwerkingen. Dit resulteerde in een langzame inclusiesnelheid van een zeer selectieve populatie van patiënten, waardoor de klinische waarde van het verdere onderzoeken van deze vraagstelling werd beperkt. Om deze reden is deze studie vervroegd gestopt. Een tweede onderdeel van de studie betrof een analyse van de immunomodulatoire en anti-angiogenetische effecten van methylnaltrexone. Dit blijft een interessant onderwerp voor toekomstig onderzoek, waarbij een recent geïntroduceerde orale mu-recepterantagonist naldemedine een patiëntvriendelijker alternatief lijkt.[12-15]

VERMOEIDHEID BIJ KANKER

Vermoeidheid is één van de bekendste symptomen van kanker en is vaak al aanwezig maanden voordat de diagnose kanker wordt gesteld.[16] Daarnaast is het een veelvoorkomende bijwerking van verschillende kankerbehandelingen. Het heeft een grote invloed op de kwaliteit van leven van patiënten met kanker, zowel tijdens als na de behandeling.[17] In hoofdstuk 7 van dit proefschrift wordt beschreven welke theorieën er bestaan over het ontstaan van vermoeidheid bij kanker en welke behandelingen hiertegen onderzocht zijn. Het ontstaan van vermoeidheid bij kanker is multifactorieel en er is geen eenduidige effectieve behandeling beschikbaar om het tegen te gaan. In studies die na het schrijven van dit artikel gepubliceerd zijn wordt aangetoond dat fysieke activiteit positief effect kan hebben op vermoeidheid.[16,18,19] Daarnaast lijkt er een plaats te zijn voor corticosteroïden bij patiënten in de palliatieve fase.[20,21] In hoofdstuk 8 wordt de correlatie tussen

vermoeidheid bij kanker en spiermassa onderzocht. Hier lijkt enig verband tussen te zijn, wat een extra argument kan zijn voor de effectiviteit van fysieke activiteit. Of het ook een oorzakelijk verband betreft zal nog verder uitgezocht moeten worden.

MISSELIJKHEID EN BRAKEN BIJ CHEMOTHERAPIE

Misselijkheid en braken zijn voor veel patiënten de meest gevreesde bijwerkingen van behandeling met chemotherapie.[22,23] In de afgelopen Jaren zijn er veel medicamenten ontwikkeld om dit tegen te gaan.[24] Veel van deze middelen zijn getest bij patiënten die hoog-emetogene chemotherapie ontvingen. In hoofdstuk 9 wordt beschreven wat er bekend is over de effecten van deze middelen bij patiënten die matig-emetogene chemotherapie ontvangen. Hier wordt duidelijk dat er nog veel informatie over deze patiëntengroep ontbreekt. Dit was reden om de MEDEA studie op te zetten. Hierin wordt de effectiviteit van de combinatie van palonosetron en dexamethason vergeleken met de combinatie van ondansetron en dexamethason en de combinatie van ondansetron met dexamethason en metocloperamide bij patiënten die matig-emetogene non-AC chemotherapie ontvangen. De resultaten van deze studie worden binnenkort verwacht.

IN CONCLUSIE

Patiënten met gevorderde stadia van kanker lopen het risico op een velerlei van symptomen die de kwaliteit van leven aan kunnen tasten. In dit proefschrift zijn een aantal hiervan beschreven. Veel van deze symptomen zijn multifactorieel bepaald, wat onderzoek naar hun oorzaak en mogelijke behandelopties bemoeilijkt. Gecombineerde inspanningen van medici en wetenschappers helpen mee om deze ingewikkelde problemen op te lossen en behandeling op maat voor de patiënt mogelijk te maken. Uit dit proefschrift blijkt dat het mogelijk is om ook bij deze kwetsbare patiëntengroep klinisch onderzoek te verrichten, zolang er een goede balans gevonden wordt tussen persoonlijke baten en potentiële risico's op nieuwe bijwerkingen.

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DANKWOORD

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LIST OF PUBLICATIONS

LIST OF PUBLICATIONS

Elisabeth C.W. Neefjes, Maurice J.D.L. van der Vorst, Susanne Blauwhoff-Buskermolen, Henk M.W. Verheul. Aiming for a better understanding and management of cancer related fatigue. The Oncologist 2013;18(10):1135-43.

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